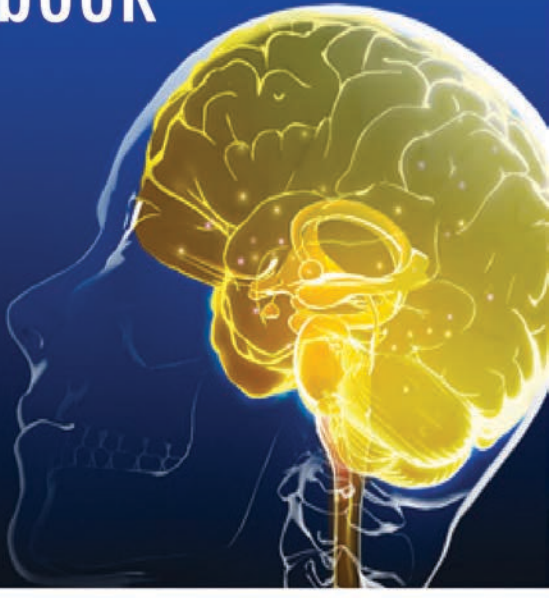
Psychiatric Drug Handbook



Lopamudra (Dhar) Chowdhury
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Psychiatric Drug Handbook

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Psychiatric Drug Handbook

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Dedicated to

The Almighty God
Our beloved son
and
Our beloved students

Preface

Psychiatry is a broad clinical discipline concerned with therapy of a myriad of psychiatric disorders.

Pharmacology is the basic cornerstone in the treatment of psychiatric disorders and often patients require lifelong therapy. Drugs used in psychiatry are unique in some aspects. These drugs have complex mechanisms of action, multiple uses and many drug interactions. As most patients undergo drug therapy for a prolonged period of time, patients often have other co-existent diseases or other co-administrated drugs. Hence, a profound knowledge of pharmacology is very essential for proper delivery of psychiatric treatment.

This book is intended to provide coverage of all important aspects of drugs used in psychiatric disorders, in an easy, concise yet comprehensive style. It will save time and certainly be very useful to the busy practitioners as well as students. Information in bullets, tables and clinical pearls at the end of chapters emphasizes important points, which can be memorized easily. Moreover, certain topics like Antidepressants, Psychiatric Drug Therapy in Special Conditions and Drug-Drug Interactions have been discussed too.

Psychiatric Drug Handbook will be of immense help for the undergraduate students in their preparation for PG entrance examinations as well as postgraduate students for their pharmacology oriented VIVA. As there are only a handful books in this domain, we hope this earnest endeavor will be user-friendly and highly helpful.

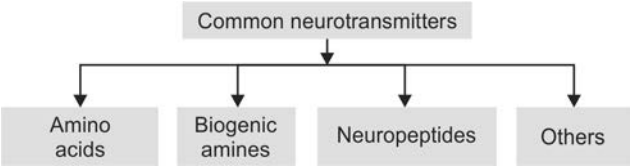
We would appreciate any comments or advice to further enrich its contents.

Lopamudra (Dhar) Chowdhury
Om Prakash Singh

Contents

Chapter

1 General Introduction



Amino Acids

1. GABA
2. Glycine
3. Taurine
4. Glutamate
5. Aspartate
6. Homocystine.

Biogenic Amines

1. Acetylcholine
2. Monoamines.

Neuropeptides

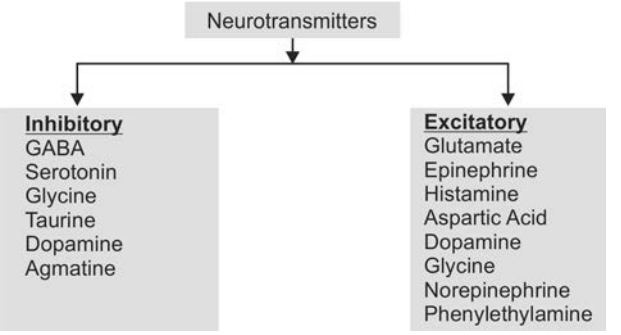
1. Substance P
2. Vasopressin
3. Enkephalin, Endorphin
4. Neurotensin
5. Oxytocin.

Others

1. ATP, cAMP
2. NO, CO
3. PGs, NH_3

Monoamines can be further subdivided into:
(i) Serotonin, (ii) Catecholamines, (iii) Histamine, (iv) Agmatine, (v) Phenylethylamine.

Catecholamines are again further subdivided into:
(a) Epinephrine, (b) Norepinephrine, (c) Dopamine.



Causes of Neurotransmitter Imbalance

1. High levels of emotional trauma or stress
2. Dietary habit
3. Neurotoxins
4. Genetics.

Expression of Neurotransmitter Imbalance

1. Depression
2. Anxiety
3. Mania
4. Aggression
5. Addiction
6. Compulsive disorders – Drugs/Gambling/Overeating
7. Insomnia
8. Epilepsy
9. Parkinsonism
10. Alzheimer's disease
11. ADHD
12. Panic disorders.

Assessment of Neurotransmitter Level in the Body

1. Plasma, serum, blood
2. CSF
3. Urine

Urinary tests of neurotransmitters are following:

GABA	Dopamine
Glycine	Serotonin
Glutamate	Epinephrine
Aspartate	Norepinephrine
Taurine	Histamine
Agmatine	Phenylethylamine

- **Neurotransmitter:** Chemical agent fulfilling following criteria:
  - synthesized within the neuron.
  - present in the pre-synaptic neuron and released due to neuronal depolarization.
  - exogenous administration of the molecule will mimic the effects of the endogenous neurotransmitter.
  - acts on post-synaptic neuronal receptor and initiate excitatory or inhibitory response.
  - termination of activity due to deactivation either in the neuron or in the synaptic cleft.
- **Neuromodulator** arises from non-synaptic sites yet modulates the response of a neuron towards a neurotransmitter, e.g. adenosine, purines, eicosanoids, NO.
- **Neurohormone** is released into the bloodstream from where it can diffuse into the extraneuronal space and exert its actions on the neuron, e.g. ACTH, FSH, LH, GH, Prolactin.

Chapter

2 Neurotransmitters in Health and Disease

DOPAMINE

Dopamine (DA) is a catecholamine consisting of a catechol-moiety attached to an ethylamine. Dopamine is related to Melanin, the dark colored pigment, formed from oxidation of dopamine/tyrosine/L-dopa, is present in skin as well as substantia nigra of brain. Dopamine being a polar molecule does not cross the blood-brain barrier (BBB). The non-enzymatic oxidation of dopamine and L-dopa results in formation of cytotoxic ROS and quinones. Thus DA and DOPA quinones attach to α-synuclein, a major component of Lewy bodies, present in the brain of patients of Parkinson's disease.

The three most important dopaminergic tracts are:

1. The nigrostriatal tract: With cell bodies in substantia nigra projecting towards corpus striatum.
   Importance:
   - Degeneration of this tract results in Parkinson's disease.
   - The nigrostriatal tract may be responsible for control of mood.
   - The D_2 receptors present at the end of the tract are blocked due to action of antipsychotic drugs; may result in parkinsonism like side effects.
2. The mesolimbic-mesocortical DA tract terminates in the ventral striatum, amygdaloid body, frontal lobe and other basal forebrain area – responsible for mediating antipsychotic effects of antipsychotic drugs.
3. Tuberoinfundibular tract: The cell bodies are in the arcuate nucleus and periventricular area of hypothalamus and project to the infundibulum and anterior pituitary.
   Importance:
   - Dopamine acts as prolactin release inhibitory factor. Hence, Dopamine receptor antagonists have side effect of hyperprolactinemia.
   - Highest concentration of Dopamine occurs in brain. Phenylalamine and Tyrosine are the precursors of DA. The

rate limiting step in synthesis is Tyrosine to DOPA by Tyrosine hydroxylase.

The action of dopamine is terminated either by reuptake mechanism, where dopamine is taken up into the pre-synaptic neuron via pre-synaptic dopamine transporter (DAT) or by metabolism. The dopamine transporter is the target of action of cocaine, methamphetamine. It is also the target of neurotoxins like MPP^+, the metabolite of MPTP which ultimately causes neuronal death, condition mimicking Parkinson's disease. Metabolism of dopamine occurs primarily by MAO-B, and less importantly by COMT. The end product of dopamine metabolism is Homovanillic Acid (HVA), concentration of which can be assessed from CSF, urine or serum.

There are 5 subtypes of Dopamine receptors D_1 to D_5 which are broadly grouped into two, D_1 and D_5 are grouped in one, D_2, D_3 and D_4 in the other. D_2 receptor found predominantly in caudate nucleus and putamen. The typical antipsychotic drugs used in Schizophrenia have antagonistic action at D_2 receptor. Bupropion blocks the dopamine transporter while dopamine containing storage vesicles are depleted irreversibly by reserpine, reversibly by tetrabenazine. D_3 selective antagonists are useful in de-addiction. Dopamine is the neurotransmitter involved in the pathophysiology of psychosis, mania, schizophrenia, depression as well as Parkinson's disease.

Norepinephrine and Epinephrine

Norepinephrine (NE) is more abundant in brain while Epinephrine derived from adrenaline is more abundant peripherally in the serum. The cell bodies of these neurons lie in the locus ceruleus of pons and project to the cerebral cortex, limbic system, thalamus and hypothalamus.

NE is synthesized from dopamine by enzymatic activity of dopamine β-OH-lase. Epinephrine is produced from NE by the enzymatic activity of phenylethanolamine-N-methyltransferase (PNMT). Termination of activity occurs due to reuptake or metabolism by MAO-A and COMT. The psychiatric drugs associated with NE are the tricyclic antidepressants and MAO-inhibitors which increase the concentration of NE (and/or serotonin) in the synaptic cleft. Both serotonin and NE are involved in the pathophysiology of depression.

Serotonin

Cell bodies of serotonergic neurons in the upper pons and midbrain project to the basal ganglia, limbic system and cerebral cortex.

Serotonin is synthesized from precursor amino acid tryptophan; availability of tryptophan is the rate limiting function and dietary variations in tryptophan can effect serotonin level in brain. Activity of serotonin is terminated either by reuptake or metabolism by MAO-A; primary metabolite being 5HIAA.

There are 7 types and 14 subtypes of receptors which leads to diverse mechanism of action. Buspiron, a potent $5HT_1A$ agonist, is used as an anxiolytic. Clozapine with significant antagonistic action on $5HT_2$ receptor is used as an antipsychotic. $5HT_3$ receptor antagonists are used as antiemetics for emesis due to various causes. Fluoxetine one of the selective serotonin reuptake inhibitors is used as an antidepressant. The serotonin system is utilized by drugs of abuse like LSD.

Serotonin has been associated with the pathophysiology of mood disorders; deficiency of 5HT causing depression while excess resulting in mania. It has also a role to play in anxiety and schizophrenia.

Histamine

Cell bodies of histaminergic neurons are located in hypothalamus and project to cerebral cortex, limbic system and thalamus.

Sedation, weight gain and hypotension may be the side effects of some psychotropic drugs due to its action on histamine receptors in brain.

Acetylcholine

In the CNS, the cholinergic neurons with cell bodies in nucleus basalis of Meynert project to the cerebral cortex and limbic system. Projection of cholinergic neurons also occurs from RAS to cerebral cortex, limbic system, thalamus and hypothalamus.

In patients with Alzheimer's disease and Down's syndrome, degeneration of neurons in nucleus basalis of Meynert has been observed.

Importance

- Acetylcholine is responsible for the pathophysiology of Alzheimer's type and other dementias.
- Anticholinergic drugs can impair learning and memory.
- In normal individuals, the activity of dopaminergic nigrostriatal pathway is balanced by the cholinergic pathway in the basal ganglia. So, in the drug induced Parkinsonism due to D_2 blockade, centrally acting anticholinergics are useful.
- Blockade of muscarinic cholinergic receptors are a common side effects of psychotropic drugs.
- Blockade of central cholinergic receptors may cause confusion and delirium.
- Increase in Acetylcholine at the synapse by preventing its breakdown by Acetylcholinesterase has been utilized in the treatment of Alzheimer's dementia; anticholinesterase drugs like Donezepil is used.
- Acetylcholine is also involved in mood and sleep disorders.

Sl. No.	*Neurotransmitter*	*Function*	*Psychopathological Implications*
1	Endogenous Opioids • Enkephalins • Endorphins • Dynorphins	Act on μ,κ,δ receptors; regulates stress, pain and mood.	May have role in addiction.
2	Corticotropin releasing factor (CRF)	Modulates response to internal and external stress.	CRF antagonists may have a role in treatment of depression.
3	Substance P	Primary afferent sensory neurons, nigrostriatal pathway involved in pain perception.	May have a role in Huntington's disease, Alzheimer's and mood disorders.
4	Neurotensin	Association with Dopamine in some nerve terminals.	Pathophysiology of schizophrenia.

Contd...

Sl. No.	*Neurotransmitter*	*Function*	*Psychopathological Implications*
5	Cholecystokinin	Triggers anxiety and panic attacks.	Pathophysiology of schizophrenia, eating disorders, movement disorders.
6	Somatostatin	GH inhibiting factor.	Huntington's disease, Alzheimer's dementia.
7	Vasopressin, Oxytocin	Regulation of mood and social behavior.	Behavioral.
8	Neuropeptide Y	Stimulates appetite.	Eating disorders.
9	GABA	Anxiolytics, Anti-epileptics act via GABA-ergic pathway.	Anxiety, epilepsy.
10	Glycine	Independent inhibitory neurotransmitter and adjunctive role for glutamate activity.	Decrease in negative symptoms of schizophrenia.
11	Glutamate	Responsible for excitotoxicity and schizophrenia. May have a role in learning and memory.	Excess NMDA activity kills neurons, may be responsible for Parkinson's disease.
12	Nucleotides	Action opposite to caffeine, terminates seizures.	Adenosine analogues may be useful as sedatives, anti-convulsants.
13	Neurotrophic factors	Neuronal growth, development and survival.	Not yet established.

Chapter

3 Hypnotics and Sedatives

Sedatives – Agents which depress CNS activity producing a calming effect or drowsiness.
Hypnotics – Agents which facilitates the onset and maintenance of sleep.

HISTORY

- Alcoholic beverages, laudanum and some herbs were used to induce sleep.
- In the middle of the nineteenth century bromide was the first agent to be used as sedative hypnotic.
- Other agents like chloral hydrate, paraldehyde, sulfonal and urethane were also used.
- Phenobarbital was introduced in 1912.
- Chlordiazepoxide synthesized by Sternbach, actions explained by Randall, was introduced for use in 1961. Thus began the era of Benzodiazepines.

All agents with sedative hypnotic effects may be broadly classified as Benzodiazepines, Barbiturates, Non-benzodiazepines or Z-compounds. Sedation may be an adverse effect of the other agents like antihistaminics, antipsychotics, or other CNS depressants like alcohol.

CLASSIFICATION

Benzodiazepines

- Ultrashort acting - ($t_{1/2}$ <1 hr), e.g. Midazolam.
- Short acting - ($t_{1/2}$ <6 hrs), e.g. Triazolam.
- Intermediate acting - ($t_{1/2}$ 6–24 hrs), e.g. Temazepam.
- Long acting - ($t_{1/2}$ >24 hrs), e.g. Diazepam.

Barbiturates

- Ultrashort acting – Thiopentone sodium, Methohexitone.
- Short acting – Pentobarbitone, Butobarbitone.
- Long acting - Phenobarbitone.

Newer Non-benzodiazepines or Z-compounds

- Zolpidem, Zaleplon, Zopiclone.

Melatonin Congener

- Ramelteon.

Others

- Buspirone, Chloral hydrate, Paraldehyde.

MECHANISM OF ACTION

Benzodiazepines

Act selectively on benzodiazepine receptor, an integral part of $GABA_A$ receptor-chloride channel complex; binding site between two α_1 and γ_2 subunits enhances presynaptic and postsynaptic inhibition by:

- Enhancing inhibitory response of GABA.
- Facilitating opening of GABA activated chloride channels.

  Also,
  - inhibits neuronal activity in the amygdala centered fear circuits.
  - inhibitory action in cerebral cortex responsible for antiseizure action.
  - inhibitory action at spinal cord level provides benefit in muscle spasms (diazepam).

Barbiturates

Act on α or β subunit of $GABA_A$ receptors in CNS, at sites different from that of Benzodiazepines and increase the duration of opening of the chloride channels.

Non-benzodiazepines

Act selectively on GABA receptor isoforms containing α_1 subunits. As α_2 and α_3 subunits of $GABA_A$ receptor are associated with anxiolytic and muscle relaxant activity, these drugs are devoid of these effects.

Others

Alcohol, intravenous anesthetic agents like propofol, etomidate, thiopentone act on β_2, β_3 subunits of the $GABA_A$ receptor.

Antagonists Bicuculline blocks GABA binding while Flumazenil is a specific competitive antagonist at the benzodiazepine binding site.

Benzodiazepines

Pharmacokinetics

- All are absorbed orally.
- Have huge lipid water distribution coefficient in non- ionized form.
- Rate of oral absorption, differ according to lipophilicity; most barbiturates and newer hypnotics are absorbed rapidly into the blood.
- Extensive distribution; crosses BBB, placental barrier, and secreted in milk.
- Plasma protein binding varies markedly, e.g. 99% for Diazepam while 10% for Flurazepam.
- Metabolized in the liver, many produce active metabolites, e.g. Flurazepam, Diazepam, Chlordiazepoxide, Alprazolam.
- Ultrarapid elimination seen with Triazolam, Midazolam
- ½ life 2–40 hrs; long ½ life as with Diazepam, Flurazepam, Lorazepam, Clonazepam.
- Metabolites are excreted in urine as glucuronide conjugates.

Actions

- Reduction of anxiety and aggression.
- Sedation and induction of sleep.
- Reduction of muscle tone and coordination.
- Anticonvulsant effect.
- Anterograde amnesia.
- Do not have antidepressant effect.
- May increase irritability and aggression in some individuals.
- Benzodiazepine withdrawal symptoms more commonly seen with short acting compounds.

Hypnosis

- Hasten onset of sleep.

- Increase total duration of sleep.
- Proportion of REM sleep is reduced.
- Duration of stage 2 NREM is increased.
- Duration of stage 4 NREM sleep is decreased.
- Growth hormone secretion remains uneffected.
- Abrupt cessation of drug may result in rebound in REM sleep.
- Tolerance develops if drug is used for > 4–6 weeks.

Sedation

Sedation is a function of GABA receptors containing α_1 subunit

- Calming effect at relatively low doses.
- Depressant effects on psychomotor and cognitive functions.
- Euphoria.
- Impaired judgement, loss of self control.
- Dose-dependent anterograde amnesia.

Other Actions

- **Anesthesia**—I.V. anesthesia, induction of anesthesia; diazepam, midazolam, lorazepam.
- **Muscle relaxation**—Inhibitory effect on polysynaptic reflexes and internuncial neurons; meprobamate, diazepam.
- **Anti-convulsant**—Clonazepam, diazepam, lorazepam, nitrazepam.
- **Respiratory and cardiovascular system**—Dose-related depression of medullary respiratory center and/or vasomotor center causing respiratory depression or circulatory collapse.

Adverse Effects

- Dizziness, headache, vertigo, ataxia.
- Amnesia, delayed reaction time, impaired psychomotor skills.
- Weakness, blurring of vision, dry mouth, urinary incontinence.
- Paradoxical actions, e.g. Irritation, anger.
- Tolerance, cross-tolerance.

Drug Interactions

- Synergistic with alcohol, other CNS depressants.
- CYP 3A4 inhibitors, e.g. Ketoconazole, Erythromycin, Cimetidine, INH, OCP retard benzodiazepine metabolism.

Uses

- Anxiety states—Generalised anxiety disorder, panic disorders, agarophobia.

- Sleep disorders—Newer non-benzodiazepine hypnotics are better.
- Seizure disorders—Diazepam, Clonazepam.
- IV anesthesia—Midazolam, Diazepam.
- Preanesthetic medication.
- In short surgical procedures, e.g. Bronchoscopy, diagnostic procedures.
- To control symptoms of ethanol or other hypnotic sedative withdrawal.

Barbiturates

- Classification
  Long acting—Phenobarbitone
  Short acting—Butobarbitone, Pentobarbitone
  Ultrashort acting—Thiopentone, Methohexitone.
- Barbiturates are substituted derivatives of barbituric acid; general CNS depressants; cause dose-dependent anxiolysis, amnesia hypnosis, anesthesia, coma, respiratory depression.

Pharmacokinetics

- ½ life 4–60 hours.
- Orally absorbed, widely distributed.
- Onset of action dependent on lipid solubility.
- Plasma protein binding varies; cross placenta.
- Termination of action depends on redistribution effect, metabolism, excretion.
- Barbiturates with low lipid solubility are excreted unchanged in urine.
- Barbiturates induce hepatic microsomal enzymes.

Uses

- Epilepsy- Phenobarbitone.
- Anesthesia- Thiopentone.
- Hypnotic- Secobarbitone.
- Congenital non-hemolytic jaundice, kernicterus.

Adverse Effects

- Hangover, tolerance, dependance, idiosyncracy, precipitation of porphyria in susceptible patients.

Newer Hypnotics

Special Features:

- Rapid onset of hypnosis.
- Minimum incidence of hangover, amnesic or psychomotor depressant action.
- Sleep pattern is minimally affected; withdrawal effect is not seen on discontinuation.
- Anti-convulsant, anti-anxiety or muscle relaxation effects are not evident specially with Zolpidem.
- Short duration of effect.
- No tolerance or dependence noted.

  Drugs—Eszopiclone, Zaleplon, Zolpidem

  Uses—Insomnia specially with prolonged sleep latency.

Melatonin Receptor Agonist Ramelteon

- Ramelteon is a specific melatonin MT_1 and MT_2 receptor agonist, acts on melatonin receptors in the suprachiasmatic nucleus.
- Advantages:

  Not associated with abuse potential, rebound insomnia, motor deficits or obstructive sleep apnea. Does not cause confusion or memory impairment on long term use in elderly.
- Mechanism of action: Reduced sleep latency, reduces the time to fall asleep, not that much effective in maintenance of sleep. May increase the total duration of sleep.
- Indications: Jet lag insomnia in elderly, insomnia associated with other neuro-psychiatric disorders.
- Pharmacokinetics: Rapidly absorbed orally, high first pass metabolism in liver. Bioavailability is low, half life is about 1–3 hours.
- Adverse effects: Headache, somnolence, dizziness, fatigue, nausea.
- Dose: 8 mg tab, 1 tab to be taken ½ hour before bed time.

Flumazenil

- Benzodiazepine analogue with minimum intrinsic activity.
- Acts on benzodiazepine receptor and reverses the activity of benzodiazepines and zolpidem, not other sedative-hypnotics.

- Used i.v. in benzodiazepine overdose, short ½ life; oral bioavailability 16%.
- After i.v. inj. action starts within seconds and lasts for 1–2 hours.
- Reverses the hypnogenic, psychomotor, cognitive and EEG effects.
- May induce panic attacks in patients with panic disorder.
- Used in benzodiazepine overdose- 0.2 mg/min i.v.

Buspirone

- Partial agonist at $5HT_{1A}$ receptors, may have activity against D_2 receptors as well.
- Slow onset of action; 1–2 weeks; no withdrawal symptoms or abuse liability.
- Anxiolytic action with minimum psychomotor impairment.
- No additive effect when given along with CNS depressant drugs.
- Orally active; active metabolite; short ½ life.
- Adverse effects: Tachycardia, paraesthesia, GI distress.

COMPARATIVE STUDY OF COMMONLY USED DRUGS

Barbiturates

Drugs	*Indications*	*Dose*	*Comments*
Phenobarbitone	Generalized tonic clonic seizure, partial seizure; sedative hypnotic.	15-20 mg 2-3 times/ day	Prolonged duration of action;Induces hepatic microsomal enzymes.
Thiopentone 25 mg/ml in solution + 1.5 mg/ml Na_2CO_3	Ultrashort acting intravenous anesthetic.	Induction dose 2.5% solution 3–5 mg/kg	Duration 5–8 min, Highly alkaline, pH 10–11.
Methohexital 10 mg/ml in solution + 1.5 mg/ml Na_2CO_3	Ultrashort acting intravenous anesthetic.	Induction dose 4–7 mg/kg	Duration of induction 4–7 min; pH 10–11.

Benzodiazepines

Drugs	*Indications*	*Dose*	*Comments*
Diazepam	As hypnotic sedative, Anticonvulsant, i.v. anesthetic.	Oral, IM, IV, Rectal 0.1–0.2 mg/kg; maximum 60 mg/day 5–10 mg tab/day; 2.5–5 mg suppository; 0.3–0.5 mg/kg for induction	Several active metabolites, Sedation, Minimal drug interactions, caution in pulmonary disease.
Lorazepam	As sedative, hypnotic.	Oral, IM, IV;1-2 mg OD/BD	more potent, profound amnesia.
Midazolam	As i.v. anesthetic for induction and maintenance; anti-hallucinatory, anticonvulsant.	IV, IM; Premedication 0.07–0.08 mg/ kg IM; induction 0.15–0.3 mg/kg; infusion 0.02–0.1 mg/kg/hr	Rapid onset of action; duration 6–8 min; liable to abuse, rapid metabolism.
Alprazolam	Anxiety disorders.	Oral	Intermediate acting, withdrawal effect, residual effect present.
Clonazepam	Seizure disorders, Acute mania.	Oral	Tolerance may develop.
Chlordia-zepoxide	Insomnia, anxiety disorders, anesthetic premedication, alcohol withdrawal.	Oral, IM, IV 0.3–0.5 mg/kg/ day; 10–25 mg tab BD	Long acting, produce active metabolites.
Flurazepam	Insomnia.	Oral; 15–30 mg/day	Long acting.
Nitrazepam	Insomnia.	Oral; 0 0.5–1 mg/ kg/day OD/BD	Long acting.
Temazepam	Insomnia.	Oral; 7.5–15 mg/ day	Intermediate acting.
Triazolam	Insomnia.	Oral; 0.125–0.25 mg/day	Rapid metabolism.

Newer Benzodiazepines

Drugs	*Indications*	*Dose*	*Comments*
Zolpidem	Insomnia	Oral; 5-10 mg at bed time	↓ REM sleep.
Zaleplon	Insomnia	Oral; 5-20 mg at bed time	Shortest acting.
Eszopiclone	Insomnia	Oral; 1-3 mg at bed time	↑ Total sleep time.

THERAPY OF INSOMNIA

Insomnia is defined as difficulty in initiating and/or maintaining sleep. Insomnia may be primary or secondary due to depression, anxiety, mania, disease states or substance abuse.

Drugs used in insomnia are:

1. Benzodiazepines—Flurazepam, Triazolam, Nitrazepam, Diazepam, Alprazolam, Temazepam.
2. Non-benzodiazepines or Z-compounds – Zolpidem, Zaleplon, Zopiclone.
3. Melatonin agonist—Ramelteon.
4. Sedative antihistaminics.

Patient can be advised about sleep hygiene along with pharmacotherapy.

Non-pharmacological Approaches

1. Sleep hygiene—Go to bed only when sleepy, avoid naps. Avoid caffeine, nicotine, alcohol, heavy or spicy food four hours before bedtime. Avoid exercise at least four hours before sleep. Maintain a sleep routine and proper sleeping environment.
2. Sleep restriction therapy—Time in bed to be reduced to that time such that 80%–90% of time is utilized in sleep.
3. Continuous positive airway pressure—For patients with sleep apnea.
4. Bright light therapy—To regularize sleep-wake cycle by resetting exposure to bright light to impede sleep at wrong time of day or night.

Pharmacotherapy

- Zolpidem, Zaleplon and Ezopiclone are preferred over benzodiazepines and are free of rebound insomnia.

- Trazodone is often used in insomnia associated with depression.
- Quetiapine in low dosages 25–100 mg/day has been used as hypnotic in patients with mood and personality disorders.

Clinical Pearls

- Diazepam is the benzodiazepine of choice in status epilepticus; also popular in treating muscle spasm and in acute alcohol withdrawal.
- Lorazepam is preferred over other benzodiazepines in treatment of delirium, also popularly used in treatment of agitation and in inducing preoperative anterograde amnesia during anesthesia.
- Alprazolam is one of the most popular anxiolytics with rapid onset of action and less sedation compared to other benzodiazepines.
- Clonazepam is the only benzodiazepine that is used as single maintenance therapy in seizure disorders and has a long duration of action.
- Buspirone used as a reserve anxiolytic, does not cause dependence or withdrawal symptoms; it reduces sexual dysfunction associated with generalized anxiety disorder or SSRI therapy.
- Benzodiazepines have been used effectively in the treatment of catatonia.

Chapter

4 Dopamine and Drugs used for Parkinson's Disease

DOPAMINE (DA)

- First synthesized in 1910.
- Consists of a catechol moiety linked to ethylamine.
- Closely related to melatonin.
- Transitional compound in the synthesis of NA and Adrenaline.
- Polar compound does not cross BBB easily.
- Amino acids phenylalanine and tyrosine are precursors.
- Dopamine is neither excitatory nor inhibitory its rather modulator; influenced by both excitatory glutamate and inhibitory GABA input.
- Drugs of abuse cause increase in DA in nucleus accumbens.
- D_2 receptor plays important role in schizophrenia. Hence, antipsychotic drugs are high affinity antagonists for the D_2 receptor.
- DA receptor agonists are now used in treatment of Parkinson's disease, restless leg syndrome and hyperprolactinemia, major limitation being lack of receptor selectivity.

Physiologic Actions

Heart

- At low concentrations, stimulates vascular D_1 receptors, causing vasodilation and reducing cardiac afterload, hence decrease in BP, increase in cardiac contractility. In high concentrations DA stimulates β receptors to increase cardiac contractility.
- In even higher concentrations circulating DA activates α receptors, hence vasoconstriction and increase in BP.

Kidney

- Binds to both D_1 and D_2 receptors.
- Renal DA causes natriuresis, increase in both renal blood flow and glomerular filtration rate (GFR).

- Activaton of D_1 receptors influence renal sodium transport and vascular hemodynamics.

Pituitary Gland

Secretion of prolactin from the pituitary gland.

Catecholamine Release

- D_2 receptor provides tonic inhibition of epinephrine release from the adrenal medulla and NE release from sympathetic nerve terminals.
- D_1 receptor stimulates release of epinephrine from adrenal medulla and NE from nerve terminals.

CNS

- Dopamine in brain is projected via four main pathways: mesolimbic, mesocortical, nigrostriatal and tuberoinfundibular pathways.

	D_1	*D_2*	*D_3*	*D_4*	*D_5*
Sites	Highest in CNS kidney, retina, CVS	Predominantly expressed in brain	Limbic areas of brain	Retina (most abundant), partly in brain	Brain
Actions	Activates c-AMP PKA pathway and interacts with A_1 receptors, NMDA receptors, Na^+K^+ATPase calnexin, caveolin	Occurs post-synaptically, regulates K^+ channels, L type and N type Ca^{+2} channels, arachidonic acid DA transporter			

- Parkinson's disease is a neurodegenerative disorder of unknown etiology, characterized by extensive degeneration of dopaminergic neurons in substantia nigra, resulting in – tremor, rigidity and bradykinesia.
- Neurodegenerative disorders are characterized by progressive and irreversible loss of neurons from specific regions of the brain,

e.g. Parkinson's disease, Huntington's disease, Alzheimer's disease, loss of neurons of hippocampus and cortex leading to impairment of memory and cognition. Parkinson's disease and Huntington's disease cause loss of neurons of basal ganglia leading to abnormalities in control of movement. Amyotropic lateral sclerosis causes degree of spinal, bulbar and cortical motor neurons.

- Abnormal proteins associated with neurogenic disorders, Alpha synuclein seen in Parkinson's disease, huntingtin seen in Huntington's disease, amyloid beta in Alzheimer's disease and TDP-43 seen in amyotrophic lateral sclerosis.
- Parkinson's disease was first described by James Parkinson in 1817 as paralysis agitans or 'shaking palsy'.
- Pathological hallmark of disease is loss of pigmented dopaminergic neurons of the substantia nigra with the appearance of intracellular inclusions known as Lewy bodies.
- Disease progresses over 5–10 years to rigid, akinetic state.
- Death occurs from aspiration pneumonia or pulmonary embolism.

DRUGS USED IN PARKINSONISM

- Dopamine precursor Levodopa in combinations with peripheral decarboxylase inhibitors, carbidopa or benztropine.
- COMT inhibitors: Entacapone, Tolcapone.
- Dopamine receptor agonists: Apomorphine, Bromocriptine, Pramipexole, Ropinirole.
- MAO B inhibitors: Selegiline, Rasagiline.
- Other medications: Amantadine, centrally acting anticholinergics, e.g. Trihexiphenydyl, Benztropine.

Drugs/Combinations in Use

- Carbidopa + Levodopa: 25 mg + 100 mg or 50 mg + 200 mg → 2-3 times daily.
- Entacapone: 200 mg with Levodopa and Carbidopa.
- Tolcapone: 100 mg with Levodopa and Carbidopa. May be hepatotoxic.
- Apomorphine: 2 mg s.c. → 6–18 mg/day causes vomiting.
- Bromocriptine: 1.25 mg → 2.5–15 mg/day. Long-term use associated with cardiac valve fibrosis.
- Pramipexole: 0.125 mg TDS.

- Ropinirole SR: 2 mg/day → 2–24 mg maximum dose per day.
- Rasagiline:– 1 mg daily → 0.5–1 mg maximum dose per day.
- Selegiline: 5 mg BD daily → 2.5–10 mg maximum dose per day.
- Trihexyphenidyl: 1 mg BD daily → 2–15 mg maximum dose per day.
- Amantadine: 100 mg BD daily → 100–200 mg maximum dose per day.

Levodopa

- L-3, 4–dihydroxyphenylalanine, the metabolic precursor of DA.
- Rapidly absorbs orally from small intestine by transport system of amino acids.
- Concentration of drug in plasma peak in 0.5–2 hours after an oral dose.
- t½ life is 1–3 hours.
- Rate and extent of absorption of levodopa depends on the rate of gastric emptying, pH of gastric juice, time of exposure to degenerative enzyme of gastric and intestinal mucosa, presence of amino acids in diet.
- Entry of the drug into CNS across the BBB is mediated by membrane transporter for aromatic amino acids.
- Levodopa is converted to DA by decarboxylation in the presynaptic terminals of dopaminergic neurons in the striatum.
- This dopamine is available for therapeutic action.
- After release it is either transported back to dopaminergic terminals by uptake mechanism or metabolized by MAO or COMT.
- Dopamine COMT → 3 methoxytyramine
  ↓ MAO ↓ MAO
  3, 4-dihydroxy-phenylacetic acid (DOPAC) 3-methoxy-4OH-phenylacetic acid (HVA)
- In clinical practise, levodopa is always administered in combination with peripherally acting inhibitor of aromatic L-amino acid decarboxylase, e.g. carbidopa or benserazide.
- If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and peripheral sites, such that < 1% of levodopa can ultimately cross the blood-brain barrier.
- 25 mg of carbidopa and 100 mg of levodopa combination given 3 times or more daily.

- Levodopa produces dramatic improvement in early phase of disease but with time its buffering capacity is lost with onset of motor complications, 'wearing off' phenomenon disabling dyskinesias and the on-off phenomenon.

Adverse Effects of Levodopa

- Nausea, motor complications, hallucinations, confusion specially in elderly occur (Clozapine and quetiapine appear to be effective).
- Activation of vascular DA receptors may produce orthostatic hypotension.
- 'Wearing off' phenomenon: Each dose of levodopa being effective only for a period of 1–2 hours; with re-appearance of symptoms increase the dose and frequency can benefit to some extent but will result in:
  i. Dyskinesia: Excessive and abnormal involuntary movements specially when plasma concentration of levodopa is high.
  ii. 'On-off' phenomenon.
  iii. Abrupt withdrawal of levodopa or other dopaminergic medications may precipitate leading to 'neuroleptic malignant syndrome' of confusion, rigidity and hyperthermia, and may be potentially lethal.

Dopamine Receptor Agonists

- Direct agonists of striatal DA receptors.
- Enzymatic conversion is not required for necessary activity; hence does not depend on functional capacities of nigrostriatal neurons.
- Longer duration of action compared to levodopa.
- Often used in the management of dose-related fluctuations in motor state.
- May modify the course of Parkinson's disease by reducing endogenous release of DA, need of exogenous L-dopa and decrease in formation of free radical.
- Ropinirole and Pramipexole are better tolerated than older agents, bromocriptine and pergolide.
- Selective activity at D_2 and D_3 receptor, no action on D_1 family.
- Absorbed orally, relieve symptoms of Parkinson's disease (like Dopa).
- *Side effects*: Hallucinosis, confusion, nausea, orthostatic hypotension, fatigue and somnolence.

- Initiated at low dose and titrated slowly.
- It is better to switch over to some other agents if somnolence is troublesome.

Apomorphine

- Dopaminergic agonist administered S.C.
- It has been used as 'rescue therapy' in management of 'on-off phenomenon' of L-dopa therapy.
- Highly emetogenic, side effects similar to other DA agonists.
- Concomitant use of apomorphine and $5HT_3$ antagonist like ondansetron is C/I due to profound hypotension and loss of consciousness.
- It has high affinity to D_4 with moderate affinity to D_2, D_3 and D_5 receptors, low affinity to D_1 receptors. It also has moderate affinity to α_{1D}, α_{2B}, α_{2C} receptors.
- Apomorphine therapy should be initiated with a 2 mg test dose in a setting where the patient can be monitored carefully.

COMT Inhibitors

- Principal therapeutic action of COMT inhibitor is to block the peripheral conversion of levodopa to 3-O-methyl DOPA, increasing both plasma t½ of levodopa as well as fraction of levodopa (each dose) which reaches CNS.
- The COMT inhibitors tolcapone and entacapone differ only in pharmacokinetic activities and adverse effects.
- Tolcapone has longer duration of action and appears to inhibit both peripheral and central COMT.
- Entacapone has a shorter duration of action and principally inhibits peripheral COMT.
- Common adverse effects are nausea, orthostatic hypotension, confusion, hallucination.
- Important adverse effects of Tolcapone is hepatotoxicity; fatal fulminant hepatic failure has been reported.

Selective MAO Inhibitors

- The isoenzyme MAO-B is the predominant form in the striatum and responsible for most of the oxidative metabolism of DA in brain.
- Two selective MAO-B inhibitors commonly used are selegiline and rasagiline.

- Produce modest beneficial effects on symptoms of Parkinson's disease.
- Selegiline has been used for years and tolerated well in younger patients with early or mild disease.
- In advanced stage, selegiline may accentuate the adverse motor and cognitive effects of levodopa therapy.
- Recently orally disintegrating tablet or transdermal patch of selegiline is being used to prevent first pass metabolism and formation of amphetamine metabolites.
- Rasagiline does not produce amphetamine metabolites; effective as monotherapy in early Parkinson's disease, significantly reducing levodopa related 'wearing off' symptoms.
- Rasagiline may have a neuro-protective role.
- MAO-B inhibitors are well tolerated but drug interactions are troublesome.

Muscarinic Receptor Antagonists

- Trihexyphenidyl (2-4 mg TDS) and Benztropine (1–4 mg BD) are currently used.
- Diphenhydramine also with antihistaminic action can also be used.
- All are adjunct drugs to dopaminergic therapy.
- *Side effects*: Sedation, mental confusion, constipation, urinary retention and blurred vision are other adverse effects.

Amantadine

- Antiviral drug against influenza A, appears to alter DA release in striatum.
- It also has anti-cholinergic activity and blocks NMDA glutamate receptors.
- Its action is modest, hence if used in initial treatment of mild Parkinson's disease, provides symptomatic relief.
- *Dose:* 100 mg BD.
- *Side effects*: dizziness, lethargy, sleep disturbance, anticholinergic effects, nausea and vomiting. Adverse effects are dose or duration related.

Clinical Pearls

- Levodopa in combination with Carbidopa is DOC as therapy.

- Dopamine receptor agonists may be used as sole therapy initially or when L-DOPA fails to produce effect.
- Anticholinergics are preferred in young patients, where tremor is the main symptom, relieves tremor and rigidity more than bradykinesia.
- Drugs in general may be grouped as symptomatic therapy and neuroprotective therapy.
- Dopamine agonists and rasagiline have neuroprotective role and are effective in both in early as well as late stages of the disease.
  - Dopamine agonists are associated with a lower incidence of response fluctuations and dyskinesias.
  - Nowadays these drugs are either administered before initiation of L-dopa therapy or along with low dose L-dopa Carbidopa combination.
  - Bromocriptine is not used due to its side effects.
  - Selective MAOIs and COMT inhibitors can be added to L-dopa carbidopa combination to minimize its dose and in response fluctuations but does not inhibit progression of the disease.
  - Atypical antipsychotics are used to relieve the confusion or psychotic symptoms developing due to dopaminergic therapy or due to the disease. Olanzapine, Quetiapine or Risperidone may be tried but Clozapine seems to be most effective.
  - High frequency brain stimulation of subthalamic nuclei/globus pallidus, Thalamotomy or Pallidectomy may be needed in patients who fail to respond to medical therapy.
- Endogenous and exogenous catecholamines are metabolized mainly by two enzymes MAO and COMT. MAO occurs within cells bound to the surface membrane of mitochondria.
- MAO abundant in NA neurons and other tissues like liver and intestinal epithelium. MAO converts catecholamines to their corresponding aldehydes; yields DOMA from NA.
- MAO oxidises other monoamines, e.g. Dopamine and 5HT.

DRUG-INDUCED PARKINSONISM

Chlorpromazine acts on all Dopaminergic receptors but specially on D_2, D_3 receptors. Dopamine activity as well as release are affected. Decrease in dopaminergic activity results in drug-induced parkinsonism, associated with tremor, rigidity and bradykinesia.

Treatment is started with a low dose of one of the centrally acting anticholinergic drugs. These drugs can improve the tremor and rigidity of parkinsonism but has little effect on bradykinesia. They have higher central: peripheral anticholinergic action.

Drugs given:

- Benztropine mesylate 1–6 mg/day.
- Biperiden 2–12 mg/day.
- Orphenadrine 150–400 mg/day.
- Procyclidine 75–30 mg/day.
- Trihexyphenidyl 6–20 mg/day.

Act by decreasing the unbalanced cholinergic activity.

Side effects: CNS Effects—Drowsiness, mental slowness, inattention, restlessness, confusion, agitation, delusions, hallucinations, mood changes.

Other effects: Dryness of mouth, blurring of vision, urinary retention, constipation, tachycardia, tachypnea, increase in IOT.

Contraindications: Prostatic hyperplasia, obstructive GI disease, e.g. pyloric stenosis angle closure glaucoma.

If medication has to be withdrawn, this should be accomplished gradually rather than abruptly in order to prevent acute exacerbation of parkinsonism.

Drug interactions—Following drugs should not be used concurrently, e.g. TCA, antihistaminics because they can precipitate complications.

The traditional antipsychotics bind D_2 50 times more avidly than D_1 or D_3 receptors; this D_2 antagonism is responsible for extrapyramidal side effects (EPS).

EPS reactions are particularly prominent with high potency D_2 dopamine receptor antagonists, e.g. Tricyclic piperazines and butyrophenones but less likely with aripiprazole, clozapine, quetiapine or resperidone.

Time of onset: 5–30 days but can occur even after a single dose.

Chapter

5 Antiepileptics

Essentials of Diagnosis of Epilepsy

- Recurrent seizures.
- Characteristic electroencephalographic changes accompany seizures.
- Mental status abnormalities or focal neurologic symptoms may persist for hours postictally.

General Considerations

The term "epilepsy" denotes any disorder characterized by recurrent unprovoked seizures. A seizure is a transient disturbance of cerebral function due to an abnormal paroxysmal neuronal discharge in the brain. Epilepsy is common, affecting approximately 0.5% of the population in the United States.

Causes are Diverse

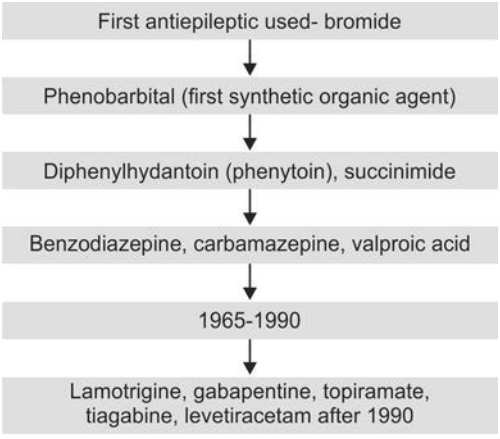
- Genetic.
- Developmental.
- Infective.
- Traumatic.
- Neoplastic.
- Degenerative.

Types of Seizures

- **Partial seizure**: Abnormal neuronal discharge restricted to a localized part of the brain; if there is no loss of consciousness it is simple; if impaired it is complex.
- **Generalized seizure**: Characterized by bilateral diffuse neuronal discharge involving both hemispheres of the brain.
- **Absence seizure**: Brief cessation of activity and loss of awareness; last for a few seconds.

- **Atypical seizure**—have a slower onset and longer duration; affects predominantly children.

Evolution of Antiepileptics



ANTIEPILEPTICS

- **Barbiturate**—Phenobarbitone, Primidone.
- **Hydantoin**—Phenytoin, Fosphenytoin.
- **Iminostilbine**—Carbamazepine, Oxcarbazepine.
- **Succinimide**—Ethosuximide.
- **Aliphatic carboxylic acid**—Valproic acid.
- **Benzodiazepines**—Diazepam, Clonazepam, Clobazam, Lorazepam.
- **Cyclic gaba analog**—Gabapentin.
- **Phenyltriazine**—Lamotrigine.
- **Newer Drugs**—Vigabatrin, Topiramate, Tiagabine, Levitiracetam, Zonisamide.

PRINCIPLES OF THERAPY

- Confirm the diagnosis.
- Assess the need for drug therapy.

- Determine the seizure type.
- Establish the etiology and evaluate other co-morbidities.
- Select appropriate antiepileptic drug.
- Start monotherapy at a lowest effective dose.
- Monitor response, adverse events and compliance.
- If seizures are controlled, continue monotherapy.
- If no response, trial monotherapy with second antiepileptic drug.
- Start antiepileptic drug at a lowest effective dose; loading dose may be required in special cases.
- Steady plasma concentration is achieved after about 5 elimination ½ lives.
- Compliance is best when given 2–3 times/day.
- Extended release formulations are better.
- Bioavailability varies between different brands.
- Clinical monitoring is essential for all patients.
- TDM is indicated in non-complaint patients, patients requiring multiple antiepileptic drugs, taking phenytoin.
- After 2–3 yrs of seizure-free period, drugs should be tapered off over a period of 2–3 months.

Early diagnosis and treatment of seizure disorders with a single appropriate agent offers the best prospect of achieving prolonged seizure free periods with the lowest risk of toxicity. Monotherapy is instituted with a single agent until seizures are controlled or toxic signs occur. When therapy with a single drug is ineffective, a second drug may be added to the therapeutic regimen. Once initiated antiepileptic drugs are typically continued for at least 2 years.

Phenobarbitone

- Barbiturate having anti-seizure activity at doses less than that of hypnotic.
- Oldest, cheapest anti-convulsant with minimum toxicity.
- Acts by inhibiting synaptic transmission via GABA-A receptor.
- Other barbiturates used as anti-seizure drugs are Mephobarbital, Metharbital and Primidone.
- Good oral absorption; peak plasma concentration is reached after a few hours; 40%–60% plasma protein bound.
- *Uses*: Generalized tonic clonic, partial seizures.
- *Side effects*: Sedation, nystagmus, ataxia confusion, agitation in elderly, irritability and hyperactivity in children. Hypoprothrombinemia

and hemorrhage observed in newborns whose mothers were treated with Phenobarbitone; may be administered vitamin K as prophylaxis.
- *Therapeutic plasma concentration*: 10–40 μg/ml.
- *Dose*: 1 mg/kg/day.

Phenytoin

- Non-sedative structural relative of Phenobarbitone.
- Effective in partial, tonic-clonic seizure, but not in absence seizure.
- Prodrug Fosphenytoin is water soluble can be administered intravenously.
- *Mechanism of action:* Blocks high frequency firing of neurons via voltage gated Na^+ channels, decrease in glutamate release at synapses.
- Oral absorption of Phenytoin is dependent on the dosage form and particle size.
- Highly plasma protein bound, 90%; t½ =12–36 hours.
- Rate of elimination is non-linear; metabolism follows first order kinetics.
- 90% Phenytoin metabolized by hepatic CYP2C 9/10, partly by CYP2C19.
- *Uses*: Generalized tonic clonic seizures, partial seizure trigeminal or other neuralgias.
- Side effects: Acute toxicity occurs with excessive dose of Fosphenytoin, e.g. cardiac dysrhythmia, hypotension with or without CNS depression. Occurrence can be minimized by maintaining dose of <150 mg of Phenytoin sodium equivalent per minute.

Chronic toxicity: Occurs with total plasma concentration > 20 μg/ml.

CNS effects: Headache, dizziness, ataxia, diplopia, behavioral changes, nystagmus.

GI effects: Nausea, vomiting, increase in hepatic enzymes.

Metabolic effects: Osteomalacia, low folate levels, peripheral neuropathy, decrease in tendon reflex.

Endocrinal: SIADH, hyperglycemia, altered metabolism of vitamin D, increase in metabolism of vitamin K (hemorrhage in newborn due to phenytoin therapy of mother).

Miscellaneous effects: Gingival hyperplasia, coarsening of facial features, hirsutism.

Hematological effects: Megaloblastic anemia, neutropenia, thrombocytopenia, lymphadenopathy, decrease in IgA.

Hypersensitive/Allergic effects: Skin, rash, fever, Steven Johnson syndrome, SLE.

Drug interactions: Increase in level of warfarin due to increase in metabolism leading to bleeding disorders or increase in metabolism of OCP resulting in unplanned pregnancy. Drug interactions involving phenytoin are either due to induction of microsomal enzymes or altered plasma protein binding.

Therapeutic plasma concentration—10-20 μg/ml. Dose–5 mg/kg/day.

Carbamazepine

- Derivative of Iminostilbene chemically related to tricyclic antidepressant like Imipramine.
- Nonsedative anti-seizure drug initially used for treating trigeminal neuralgia.
- *Mechanism of action*: Limits the repetitive firing potentials of neurons by delaying the recovery of inactivated state of voltage sensitive Na^+ channels.
- Active metabolite, onset of action may be delayed, normally 6–8 hours.
- 70% plasma protein bound.
- Orally absorbed, slow distribution, slow elimination.
- t½ about 36 hours.
- Completely metabolized by CYP3A4; can induce hepatic microsomal enzymes.
- *Uses*: Trigeminal neuralgia, glossopharyngeal neuralgia, tabetic pain (lightning type), partial and tonic clonic seizures, bipolar disorders.
- *Adverse effects*: CNS effects: Vertigo, ataxia, diplopia, drowsiness, blurred vision, dizziness, confusion, headache.
- *GI effects*: Nausea, vomiting, diarrhea, transient rise of hepatic transaminases.
- *Hematological effects*: Aplastic anemia agranulocytosis, idiopathic blood dyscrasia, leukopenia.

- *Hypersensitivity reactions:* Skin rash, eosinophilia, lymphadenopathy, splenomegaly.
- *Late complications*: Water retention, SIADH and hyponatremia specially in cardiac patients.

Contraindication: First trimester of pregnancy, bone marrow suppression, history of allergy to tricyclic compounds; used with caution in cardiac disease.

Drug interactions: Due to induction of CYP3A4 microsomal enzymes, may enhance metabolism of phenytoin, haloperidol. May decrease plasma concentration of other anticonvulsants like Valproate, Tiagabine, Topiramate, Lamotrigine.

- Therapeutic plasma concentration: 6–12 μg/ml.
- Dose: 1–2 g/day in adults; 15–25 mg/kg/day in children.

Valproic Acid

- Simple branched chain carboxylic acid effective in inhibiting a variety of seizures.
- Fully ionized at body pH, the active form of the drug is valproate ion.
- *Mechanism of action*: Inhibits high frequency repetitive firing of neurons by affecting Na^+ currents (Mechanism of action in partial seizure). Blockade of NMDA receptor mediated neuronal stimulation. Facilitates the enzyme glutamic acid decarboxylase (GAD) responsible for GABA synthesis. In high concentration inhibits GABA transaminase thereby preventing breakdown of GABA and increasing its concentration. May also influence inhibition on GABA transporter GAT-1. Slight reduction in T type Ca^+ current is also seen.
- *Uses*: Absence seizure, generalized tonic clonic seizure, myoclonic seizure, partial seizure.
  Other uses: Bipolar disorder, migraine prophylaxis, bipolar depression; as adjunct in psychosis and schizophrenia.
- Well absorbed orally, BA 80%.
- Peak plasma concentration in 2 hours.
- 90% plasma protein bound.
- Available in both tablet and syrup formulation.
- t½ 9–18 hours; elimination is slow, 95% hepatic metabolism.

Adverse effects

- *GI effects*: Most common, anorexia, nausea, vomiting.

- *CNS effects*: Ataxia, tremor, dizziness, headache, sedation, increased appetite.
- *Miscellaneous*: Rash, alopecia, weight gain, idiosyncriatic hepatotoxicity and thrombocytopenia.

Teratogenic effects: Spina bifida, increase in incidence of CVS, orofacial and digital abnormalities, other neural tube defects.

Drug interactions: Inhibits metabolism of several drugs like phenobarbitone, phenytoin, carbamazepine. It inhibits the metabolism of drugs primarily metabolized by CYP2C9, e.g. Lamotrigine, Lorazepam. Concurrent use of clonazepam may induce status epilepticus.

Contraindications: Pancreatitis, serious liver disease, first trimester of pregnancy.

- Plasma therapeutic concentration = 50–100 μg/ml.
- Dose: 25–30 mg/kg/day.

Ethosuximide

- Succinimide with selective action in absence seizure.
- *Mechanism of action*: Reduces low threshold T-type Ca^{+2} current in thalamic neurons. Does not inhibit sustained repetitive firing or does not have any effect on GABA concentration.
- Oral absorption complete, peak action in 3 hours.
- Not significantly plasma protein bound.
- 75% of drug metabolized by hepatic microsomal enzymes.
- t½ is about 40–50 hours.
- *Adverse effects*—GI effects: Nausea, vomiting and anorexia.
  CNS effects—drowsiness, lethargy, headache, dizziness, Parkinson like symptoms, photophobia, restlessness, agitation.
  Hypersensitivity—Urticaria, skin reactions, Steven-Johnson syndrome.
  Hematological effects—Eosinophilia, leukopenia, thrombocytopenia, pancytopenia.
- *Therapeutic plasma concentration*: 40–100 μg/ml.
- *Oral dose:* 250–500 mg/day.

Gabapentin

- Consists of a GABA molecule covalently bound to a lipophilic cyclohexane ning.

- High lipid solubility.
- Closes N and P/Q presynaptic calcium channels and decreases release of neurotransmitter, decreasing excessive neuronal activity. May promote non-vesicular release of GABA.
- Absorption after oral administration, excreted unchanged, mainly in urine.
- ½ life 4–6 hours.
- Effective for – partial seizure, postherpetic neuralgia, restless leg syndrome, migraine, chronic/neuropathic pain, bipolar disorder.
- *Side effects*: Well tolerated.

GI effects: Somnolence, dizziness, ataxia, fatigue, peripheral edema, usually resolve in 2 weeks of onset.

Drug interactions: Antacids reduce bioavailability; naproxen, morphine, hydrocodon may increase BA.

Lamotrigine

- May have actions in addition to regulating recovery from inactivation of Na^+ channels – possibly involves inhibition of glutamate and aspartate release.
- Completely absorbed from GIT.
- Metabolized by glucuronidation.
- ½ life 15-30 hours, elimination half life is approximately doubled in concomitant valproate therapy.
- *Indications*: First line therapy in bipolar depression, prevents relapses of BPD

  To be preferably avoided in first trimester of pregnancy, if used, dose to be decreased. Effective in partial/generalized tonic-clonic seizures.
- *Side effects*: Rash is an important adverse effect, specially common in pediatric age group. Dizziness, blurred vision/diplopia, nausea, vomiting, Steven-Johnson syndrome, DIC may also occur.

Levetiracetam

- Mechanism of action not exactly known.
- Inhibits partial and secondary generalized tonic-clonic seizures in kindling model.

  Uses: As adjunct to therapy of partial seizures, myoclonic seizures, primary generalized tonic-clonic seizures, neuropathic pain, mania.

- Rapidly and almost completely absorbed.
- Not bound to plasma protein, not metabolized, neither induces nor inhibits CYP450 enzymes.
- 95% of the drug and its inactive metabolite are excreted in the urine.
- Used in neuropathic pain or bipolar disorder refractory to treatment.
- Well tolerated.
- *Side effects*: Somnolence, asthenia, dizziness. RBC count and Hb% may decrease.

Tiagabine

- Anticonvulsant acting by selectively inhibiting GABA uptake.
- Rapidly absorbed, extensively bound to plasma protein.
- Metabolized by liver.
- ½ life of 8 hours.
- *Uses*: Add on therapy of refractory partial seizure, anxiety disorders, neuropathic/chronic pain.
- *Dose*: 32–56 mg/day in epilepsy, 2–12 mg/day in pain disorders.
- *Side effects*: GI effects, dizziness, somnolence, tremor.

Topiramate

- Decrease voltage gated Na^+ current in cerebellar granule cells, potentiates GABA, inhibits glutamate release.
- Broad spectrum anti-seizure activity.
- Rapidly absorbed after oral administration.
- Effective as monotherapy in – refractory partial seizures, refractory tonic clonic seizures, migraine prophylaxis; as adjunct in BPD, psychotropic drug induced weight gain.

Zonisamide

- Inhibits T type Ca^{+2} channels prolonging the inactivated state of voltage gated Na^+ channels, facilitates dopamine and serotonin release.
- Well absorbed orally.
- Effective in partial and secondary tonic clonic seizures.
- Well tolerated; sulphonamide derivative; sedation, depression, irritability, headache, kidney stones, increased serum creatinine and BUN. Life threatening rashes can occur.

Clonazepam

- Benzodiazepine, potentiate GABA induced Cl^- flux to produce sedation.
- Oral absorption good.
- 85% plasma protein bound.
- t½ 24 hours, metabolized in liver, excreted in urine.
- *Side effects*: Sedation, dullness (minimized by starting at low dose). Lack of concentration, confusion, irritation, temper and behavioral changes in children, ataxia and motor disturbances are dose related.
- Flumazenil or concurrent valproate therapy can precipitate seizures.
- *Uses:* Absence seizure, myoclonic and akinetic seizure , panic disorder, other anxiety states, insomnia, catatonia.
- *Contraindications*: Severe liver disease, angle closure glaucoma.
- *Dose*: 0.5–5 mg TDS in adults; 0.02–0.2 mg/kg in children.

Clobazam

1, 5-benzodiazepine introduced as anxiolytic found to be an anti-epileptic, acts by GABA facilitation.

- BA-90%.
- t½ - 18 hours, active metabolite is produced.
- Used as an adjuvant antiepileptic in GTCS; absence myoclonic and atonic seizures.

Diazepam

Drug of choice in emergency control of seizures.

0.2–0.5 mg/kg slow I.V.; max 100 mg/day; in status epilepticus, tetanus, eclampsia, convulsant drug poisoning.

Side effects: Respiratory depression, hypotension, thrombophlebitis.

Primidone

- May be more effective than Phenobarbitone.
- Metabolized to active metabolites.
- Completely absorbed.
- Not highly plasma protein bound.
- Therapeutic plasma concentration: 8–12 μg/ml.

- ½ life of parent drug 30–40 hours; ½ life of metabolites 4–20 days.
- Use and toxicity similar.

DRUG THERAPY OF STATUS EPILEPTICUS

- Maintenance of airway.
- 50% dextrose (25–50 ml) i.v.
- If seizures continue Lorazepam 4 mg bolus dose at the rate of 2 mg/min repeated every 10 minutes.
- If required Diazepam 10 mg i.v. over 2 min repeated after 10 minutes.
- Phenytoin (Fosphenytoin) 10–20 mg/kg given i.v. at a rate of 50 mg/min.
- If seizure still continues, Phenobarbital 10–20 mg/kg i.v. slowly or 50 mg/min intermittently. Alternatively i.v. valproate 25–30 mg/kg over 15 minutes, then 100 mg/hr.
- I.V. Midazolam in refractory cases in a loading dose of 0.2 mg/kg, followed by infusion of 0.05–0.2 mg/kg/hr.
- Propofol 1–2 mg/kg i.v. bolus, followed by infusion of 2–15 mg/kg/hr.
- After management of status epilepticus, long-term management of seizures to be done.

Chapter

6 Antidepressants

ANTIDEPRESSANTS

Depression and anxiety disorders involve variations in mood, behavior, cognition and somatic function and are amenable to pharmacological treatment. Depressive episodes are characterized by sadness, pessimism, lack of concentration, insomnia, mental slowing, feeling of guilt and worthlessness.

Antidepressants used are as follows:

1. **Selective Serotonin Reuptake Inhibitors (SSRIs)**—Sertraline, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram, Paroxetine.
2. **Selective Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)**—Venlataxine, Duloxetine, Desvenlafaxine.
3. **Atypical Antidepressants ($5HT_2$ Receptor Antagonists)**—Duloxetine, Mirtazapine, Mianserin, Bupropion, Nefazodone, Trazodone.
4. **Tricyclic and Tetracyclic Antidepressants**:

Amitriptyline	Amoxapine
Clomipramine	Nortriptyline
Imipramine	Protriptyline
Doxepine	Maprotiline.

5. **Monoamine Oxidase Inhibitors**:
   MAO – A inhibitor – Moclobemide
   MAO – B inhibitor – Selegiline.
6. **Newer Antidepressants**—Atomoxetine, Agomelatin, Vilazodone.
   Mechanism of action—The reuptake inhibitors increase the respective neurotransmitter levels by inhibiting the transporters: SERT (serotonin transporter) or NET (norepinephrine transporter) or both. Tricyclic antidepressants increase 5HT and NE level by inhibiting their reuptake while the MAOIs act by inhibiting the metabolism of monoamine neurotransmitters, 5TH, Norepinephrine and/or Dopamine. MAO-A and MAO-B are involved in metabolising both 5HT and NE and are present in mitochondria of most neurons. MAO-B is present in serotonergic neurons.

Long Term Effects of Antidepressants

- Increase in adrenergic and serotonergic receptors.
- Increased receptor functioning.
- Increase in neurotrophic factors.
- Increase in neurogenesis.

There is usually a period of 'therapeutic lag' of about 3–4 weeks, before antidepressant action becomes evident. After successful initiation of therapy, a maintenance therapy of 6–12 months is generally necessary after which the drug is gradually tapered off. Major depression of >2 years duration, often require life long therapy.

DISCUSSION

Antidepressants are most widespread in use.

- Popularity rests on (i) efficacy, (ii) broad spectrum of activity, (iii) relative safety, (iv) easy use.
- SSRIs and SNRIs are also used in prescription of generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, obsessive compulsive disorder, bulimia, premenstrual dysphoric disorder.
- Off label use → negative symptoms of schizophrenia, agitation of dementia, impulse control disorders and borderline personality disorders, treatment of postmenopausal vasomotor symptoms and migraine prophylaxis.
- Other uses include neuropathic pain, fibromyalgia, smoking cessation, enuresis.
- Advantages of newer antidepressants, e.g. SSRI, SNRI, bupropion, mirtazapine – once daily dose, safety in overdose, economic or cost-effective.
- Newer additions like Agomelatine (melatonin 1, melatonin 2 agonist and $5HT_{2C}$ antagonists) have less side effects and induce sleep while triple uptake inhibitor, e.g. Tesofensive, which inhibits reuptake of NE, serotonin and dopamine act rapidly and do not cause weight gain.
- As there are a number of antidepressants available, choice depends on:
  - Patient parameters: Age, sex, subtype of depression, medical status.
  - Drug parameters: Safety, side effects and cost.

- Atypical depression respond better to MAOIs than TCAs. Also to SSRI and bupropion which are the first line agents of drug therapy. Melancholic depression is more likely to respond to TCA, SNRI, Venlafaxine, Mirtazapine than SSRI. Psychotic depression responds to ECT. MAOIs are used in treatment resistant depression.
- In aged patients toxicity due to antidepressant therapy is more likely due to:
  - Increase in fat: muscle ratio.
  - Decrease in hepatic function, multiple medications.
  - Decrease in renal clearance.
- SSRIs like citalopram, escitalopram, sertraline are better tolerated and have least chance of drug-drug interactions.
- Regarding gender preponderance, men tolerate and respond better with Venlafaxine, Duloxetine, or TCA while women respond well to SSRI or $5HT_2$ antagonist.
- Other associated medical conditions may influence the choice:
  - Patients with pain conditions → Duloxetine, Venlafaxine, TCA.
  - Patients with H/O seizure/stroke/head injury → SSRI, Venlafaxine.
  - Patients with arrhythmia/coronary artery disease → SSRI, not TCA/MAOI.
  - AIDS patients → Nefazodone may increase toxicity of Protease inhibitor.
- According to safety, drugs may be rated in descending order SSRI → SNRI → TCA → MAOI.
  - Depression with insomnia → Mirtazapine/Tertiary amine TCA.
  - Depression with anxiety → SSRI/SNRI + hypnotic.
  - Depression with hypersomnia → Bupropion and fatigue.

PRINCIPLES OF ANTIDEPRESSANT THERAPY

- Start with smallest efficacious dose.
- Symptoms should improve after 4 weeks therapy. If benefits are partial, dose should be increased every two weeks assessing response, tolerability or appearance of side effects.
- Efficacy of antidepressant cannot be assessed before four weeks, some patients may show significant response after two weeks but majority require about six weeks to respond.

- Patients should continue therapy for at least 6 to 12 months at the dose to which they respond.
- Continuation of therapy reduce the incidence of relapse.
- Maintenance therapy should be continued unless pronounced side effects are present.
- Long-term therapy is particularly recommended in patients who had three or more serious depressive episodes or two episodes in last 5 years.
- Patient and his family members should be educated about adherence to therapy without changing the dosage or discontinuation to prevent depression associated progressive brain changes.

SSRI

- First SSRI to be introduced was Fluoxetine (1987); others soon followed, e.g. Paroxetine, Sertraline, Citalopram, Escitalopram, Fluvoxamine, Nefazodone.
- All SSRIs are effective in the treatment of not only depression but a variety of disorders, e.g. OCD, panic disorder, generalized anxiety disorder, social anxiety disorder, eating disorder and premenstrual dysphoric disorder.
- Most widely prescribed drugs specially in the treatment of major depressive and anxiety disorders.
- *Mechanism of action:* SSRIs selectively inhibit the reuptake of 5HT by inhibiting the action of Na^+K^+ATPase dependent serotonin transporter (SERT) in the presynaptic neuron and thereby increase the concentration of 5HT in the synapse. Though selectivity is not absolute eg. Fluoxetine blocks 5HT reuptake 200 times more than that of NE.
- Moreover with chronic administration there is decrease in sensitivity of somatodendritic and terminal $5HT_{1A}$ autoreceptors which is also responsible for antidepressant action.
- In addition SSRIs increase transcription of neurotrophic factors including brain-derived neurotrophic factors (BDNF) which is responsible for increase in synaptogenesis, neurogenesis and resilience of neurons.

- Compared to TCAs, SSRIs have minimum affinity for H_1, H_2, α_1 and muscarinic receptors.

Pharmacokinetics

	t½	*Plasma Protein Binding*	*Metabolite – Active Metabolite*	*Peak Plasma Level*
Fluoxetine	4–6 days	94%	+	6-8 hours
Norfluoxetine	7–9 days		Metabolite of fluoxetine	
Paroxetine	21 hours	99%	NA	2–8 hours
Sertraline	26 hours	95%	+	6–8 hours
Citalopram	35 hours	94%	NA	4–6 hours
Escitalopram	27–32 hours	56%	+	5 hours
Fluvoxamine	15 hours	77%	NA	2–8 hours

- Plasma t½ in average is about 22–33 hours, with Fluoxetine and Norfluoxetine having longest t½ life (48–72 hours).
- Plasma protein binding 80–98%.
- Potent inhibitors of CYP2D6, resulting in drug interactions (Fluoxetine, Paroxetine), Fluvoxamine inhibitor of CYP3A4 while Citalopram, Escitalopram and Sertraline have few drug interactions.
- Relatively safe drugs with minimum adverse effects.
- They are devoid of cardiovascular, anticholinergic or neurological side effects.

All SSRIs are metabolized in the liver by the cytochrome P450 enzyme. Hence, there is chance of drug interactions. Fluvoxamine is the most problematic, interacts with theophylline, clozapine, alprazolam, clonazepam, etc. Fluoxetine, Paroxetine interacts with opiate analogues. Sertraline, Citalopram and Escitalopram are least involved in drug interactions.

Pharmacodynamics

	5HT Reuptake Inhibition	*Inhibition of NE Reuptake*	*Inhibition of Dopamine Reuptake*	*Others*
Fluoxetine	+++	+		Binds to $5HT_{2C}$ receptor.
Paroxetine	++++	+		Significant anti-cholinergic action.
Sertraline	+++	+	+	
Citalopram	++++	+/–	+/–	Slight H_1, GABA, benzodiazepine action at receptors.
Escitalopram	+++	+/–	+/–	Do

Uses

First-line therapy for:

- **Depression—**SSRIs are the drugs of first choice. They are specially considered in:
  - Depression associated with suicidal ideation.
  - Depression during pregnancy and postpartum.
  - Depression in elderly and medically ill.
  - Depression in children – only Fluoxetine can be used under close supervision.
- **Anxiety disorders**
  - Obsessive compulsive disorder.
  - Panic disorder.
  - Social anxiety disorder.
  - Post-traumatic stress disorder.
  - Generalized anxiety disorder.
- **Eating disorders**
  - Bulimia nervosa.
  - Anorexia nervosa.
  - Obesity.
- **Premenstrual dysphoric disorder.**

Others

- Anger or impulsive behavior associated with personality disorders.

- Pain disorders, e.g. diabetic neuropathy, fibromyalgia.
- Premature ejaculation.
- Paraphilias.
- Autism.

Adverse Effects

- *GI adverse effects*: Nausea, diarrhea, cramping, heart burn, flatulence, dyspepsia. Sertraline and Fluvoxamine are specially responsible. GI effects gradually reduce in 2–4 weeks of therapy.
- *Weight gain*: Initially there is appetite and weight loss, peaking at 20 weeks, coming to baseline gradually. $^1/_3$rd patients on SSRI gain weight, which is resistant to diet and exercise regimen. Paroxetine is specially responsible.
- *CNS symptoms*: Headache, anxiety, insomnia, agitation, probably due to activation of diffuse serotonergic pathways.
- Sleep effects, e.g. vivid dreams, nightmares, restless legs, nocturnal myoclonus, insomnia, hypersomnia. Chronic use leads to emotional blunting, increased yawning. Rarely seizures and EPS associated with dystonia, tremor, rigidity.
- *Anticholinergic effects*: Dry mouth, constipation and sedation are seen due to Paroxetine.
- Hematologic: SSRIs can cause functional impairment of platelet aggregation manifested as easy bruising or prolonged bleeding.
- *Endocrinal*: SSRIs can decrease prolactin levels and can cause mammoplasia and galactorrhea in either sex. Breast changes are reversible.
- *Serotonin syndrome*: Co-administration of SSRI and MAOIs or lithium or tryptophan can increase plasma serotonin level resulting in diarrhea, agitation, restlessness, autonomic instability, shivering, rigidity, delirium. Treatment is supportive.
- *Others*: Hypoglycemia specially in diabetic patients.Hyponatremia, SIADH, sweating and various types of rashes are other adverse effects.

Drugs to be avoided due to drug interactions:

1. MAOIs → serotonin syndrome.

2. TCAs, type IC antiarrhythmics, Benztropine, many antipsychotics – Plasma concentration increases due to CYP2D6 inhibition specially by Fluoxetine, Paroxetine, Sertraline.
3. Theophylline, benzodiazepine, haloperidol – increases in concentration when co-administered with Fluvoxamine.
4. SSRI + Alprazolam/Triazolam/Trazodone → increases drowsiness.
5. Citalopram and Escitalopram produce minimum drug interactions.

Special remarks:

- SSRI discontinuation may lead to withdrawal symptoms.

Serotonin NE Reuptake Inhibitors

- Venlafaxine, Desvenlafaxine, Duloxetine and Milnacipram are selective serotonin and NE reuptake inhibitors.
- Venlafaxine and its major metabolite Desvenlafaxine, more potent inhibitor of reuptake of NE. Duloxetine more potent compared to Venlafaxine, is the first line therapy for both melancholic and psychotic depression, even resistant depression.

Advantages

- Do not have activity on muscarinic nicotinic, histaminergic, opioid or adrenergic receptors.
- Weakly plasma protein bound and not potent inhibitors of CYP P450 enzymes.
- Hence minimum chance of drug interactions and adverse effects.
- Better efficacy than SSRIs in the chronic pain therapy.
- All SNRIs bind to serotonin and NE transporters but unlike the TCA they do not bind to other receptors.
- t½ of 11-12 hours; once daily dosing.
- Minimum plasma protein binding except Duloxetine, which undergoes extensive hepatic metabolism.
- *Mechanism of action*: Similar to TCA.

Uses

1. Major depression – Venlafaxine, Desvenlafaxine, Duloxetine.
2. Generalized anxiety disorder – Duloxetine.
3. Social anxiety disorder – Venlafaxine.

4. Post-traumatic stress disorder, even resistant to SSRI – Venlafaxine.
5. Neuropathic pain, fibromyalgia, diabetic neuropathy – Duloxetine, Milnacipram.
6. Childhood and adult attention deficit/hyperactivity disorder – Venlafaxine.
7. Stress urinary incontinence – Duloxetine.
8. Vasomotor symptoms of menopause – Desvenlafaxine.

Adverse effects: Better tolerability. Side effect profile similar to SSRIs like nausea, constipation, headache, insomnia and sexual dysfunction. Venlafaxine may cause sustained diastolic hypertension, hence available in extended release form.

1. GI effects: Especially nausea.
2. Non-adrenergically mediated treatment –emergent hypertension.
3. Increase in heart rate about 1–4 beats/minute.
4. Hepatotoxicity: Especially Duloxetine.
5. Anticholinergic like side effects: Dry mouth, constipation, urinary retention.
6. Drug interactions: Serotonin syndrome when co-administered by MAOIs. There should be two weeks gap before starting other drug. Venlafaxine can increase haloperidol level.

   Pharmacokinetic drug interactions are minimum with Milnacipram.

Discontinuation—Withdrawal symptoms are especially common with drugs with short ½ life like Venlafaxine, Desvenlafaxine. Suddenly may result in significant dizziness, paraesthesia as withdrawal symptoms. Hence drug should be tapered off, if administered for more than 7 days.

5HT$_2$ Receptor Antagonists

- Trazodone and Nefazodone act as antagonists at post-synaptic 5HT$_{2A}$ and 5HT$_{2C}$ receptors, Nefazodone being the most potent.
- Mechanism of action: Paradoxical down regulation of 5HT$_2$ receptors and antagonism responsible for anti-depressant and anti-anxiety effect.
  - Block reuptake of 5HT and NE (more weakly) to some extent.
  - May stimulate 5HT$_{1A}$ receptors.
  - Chlorophenylpiperazine a major metabolite of these drugs is a direct agonist of 5HT$_{2C}$ receptors.
- Structurally different from other anti-depressants.

- Pharmacokinetics of Nefazodone (analog of Trazodone) – rapidly and completely absorbed after oral administration.
  - t½ is 2–4 hours but steady plasma concentration is maintained for 4–5 days due to active metabolites.
- *Indications:* Major depression – efficacy more than TCA.
  - generalized anxiety disorder.
  - panic disorder.
  - premenstrual dysphoric disorder.
  - chronic pain.
  - post-traumatic stress disorder.
  - chronic fatigue syndrome.
  - depression resistant to other therapy.

  Not effective in treating obsessive compulsive disorder.
- *Contraindications*: History of stroke, heart attack.
  - dehydration/hypovolemia.
  - pregnancy, lactating mothers: Patients on antihypertensive therapy or on MAOIs.
  - severe liver disease.
- *Drug interaction:* Inhibition of CYP 3A4 leads to increase in concentration of Triazolam, Alprazolam, Digoxin, Haloperidol.
- *Adverse effects*: Sedation, nausea, dizziness, weakness.
  - Insomnia, agitation.
  - Visual trails; patients often see after image of moving objects.
  - Hypotension, often postural (due to mild antagonistic action on α_1 receptors).

  Adverse effects are slightly lower with Nefazodone compared to Trazodone.
  - priapism associated with Trazodone therapy is seen in younger males. Sexual adverse effects are rare with Nefazodone.

  Withdrawal: Though discontinuation symptoms are uncommon, it is advisable to gradually decrease dose by 50-100 mg/week and taper off.

Bupropion

- Antidepressant which may be used as first line therapy but also used as add-on therapy to SSRIs.
- Advantages over other antidepressants:
  - minimum sedation, sexual dysfunction, orthostatic hypotensive adverse effects.

  - long term treatment/acute therapy is associated with moderate weight loss instead of weight gain (does not stimulate appetite).
  - discontinuation of therapy is not associated with withdrawal symptoms.
  - relatively safe in overdose.
- Structurally related to amphetamine.

Pharmacokinetics

- Well absorbed orally, peak plasma concentration occurs in 2 hours.
- t½ is about 8–40 hours (average 12 hours), extended release formulation can be administered once daily.
- Active metabolite hydroxybupropion – metabolized by CYP 2B6 enzymes.

Mechanism of Action

- Bupropion and hydroxybupropion are modest reuptake inhibitors of both NE and dopamine.
- Bupropion also causes pre-synaptic release of catecholamines and binds to dopamine transporter in brain.
- It has no action on the serotonergic system.
- Effect of bupropion in smoking cessation may be due to dopamine reward pathways or due to inhibition of nicotinic (ACh) receptors.

Indications

- Depression – safe in cardiac patients.
- Bipolar disorders – less likely than TCAs to produce mania.
- Smoking cessation – FDA approved, 300 mg/day.
- Seasonal affective disorder.
- ADHD – bupropion is metabolized to several amphetamine like products.
- As add-on therapy with SSRI, to augment anti-depressant action of SSRI and to counter act their sexual side effects.
- Cocaine detoxification – to decrease craving in subjects withdrawn from cocaine.

  Not useful in anxiety/panic disorders.

Contraindications

- History of epilepsy/seizure.
- Organic brain disease.
- Head injury.
- Pregnant/lactating women – severe anxiety or panic disorder.

Adverse Effects: Favorable Side Effect Profile

- Most common → insomnia, tremor, dry mouth, headache, nausea.

- Seizure – risk increases with alcohol or cocaine use or recent benzodiazepine withdrawal. Minimized by using sustained release preparations.
- Psychotic symptoms including hallucinations, delusions, delirium, catatonia.

Drug Interactions

- Should not be combined with MAOIs, because of hypertensive crisis. A minimum period of 14 days should be maintained before introduction of therapy.
- Coadministration with Levodopa or other Anti-Parkinsonism drug may increase adverse effects.
- Coadministration of Metoprolol causes sinus bradycardia.

Mirtazapine

- Tetracyclic chemical agent, unrelated to TCA, antagonistic at central pre-synaptic α_2 - adrenergic receptors.
- *Mechanism of action:* Antagonist of central pre-synaptic α_2 adrenergic receptors.
  - Increase in NE release.
  - 5HT release occurs secondary to stimulation of α_1 receptors on 5HT cell bodies.
  - Blocks $5HT_2$, $5HT_3$ and H_1 receptors, moderately blocks muscarinic receptors.
  - Does not significantly block post-synaptic α adrenergic receptors, hence postural hypotension does not occur.

Pharmacokinetics

- Well absorbed from GIT.
- Metabolized to several active metabolites by several CYP450 enzymes (CYP2D6, 3A3/4, IA2) but neither induce nor inhibit the enzymes.

Indications

- Mild/severe/recurrent depression; including atypical and seasonal depression.
- Depression with severe/long standing insomnia.
- Elderly depressed patients or depressed patients on cancer chemotherapy (combats insomnia, increases appetite, prevents vomiting).
- To augment anti-depressant action of SSRI or Venlafaxine.

- Patients with depression and co-morbid generalized anxiety disorder.
- Panic disorder with/without concurrent depression.

Contraindications

- Coadministration of CNS depressants including alcohol.
- Pregnant or nursing mothers.
- Hypercholesterolemia/hypertriglyceridemia.
- Infectious diseased condition.
- Driving/operating dangerous machinery.

Adverse Effects

- Somnolence, most common side effects potentiates other CNS depressant drugs.
- Dizziness.
- Increase in appetite and weight gain.
- Increase in serum cholesterol and triglycerides.
- Neutropenia.
- Orthostatic hypotension/hypertension.
- Fairly safe in overdose. Most common adverse effect is sedation.
- *Drug interaction:* MAOIs → hypertensive crisis (two weeks gap necessary).
  - CNS depressants → increase in somnolence.

Sl. No.	*Drugs*	*Mechanism of Action*	*Adverse Effects*	*Uses*
1	Trazodone	Weakly blocks 5HT uptake, weak $5HT_2$ antagonistic activity, α_1 adrenergic blocking action.	Sedation, bradycardia, postural hypotension, priapism.	Major depression.
2	Mirtazapine	Blocks α_2 auto and hetero receptors, increases both NA and 5HT release, concurrent block of $5HT_2$, $5HT_3$ receptors, additional H_1 receptor blockade.	Sedation, increase in appetite, weight gain, rarely agranulocytosis.	Do

Contd…

Sl. No.	*Drugs*	*Mechanism of Action*	*Adverse Effects*	*Uses*
3	Mianserin	Blocks presynaptic α_2 receptors, increase in NA antagonistic action on $5HT_2$, $5HT_1$ and H_1 receptors.	Sedation, anxiolysis, seizure, liver dysfunction, blood dyscrasia.	Depression with anxiety.
4	Bupropion	Inhibitor of NA and Dopamine reuptake, Non-sedative antidepressant, prolonged elimination t½, 11 hours.	Agitation, insomnia, dry mouth, seizures in high dose.	Smoking, cessation.
5	Tianeptin	Increase in 5HT uptake but has anti-depressant and anti-anxiolytic effect.	Insomnia/ drowsiness, dry mouth, body ache, tremor.	Depression with anxiety.
6	Amineptin	Increase in 5HT uptake but has anti-depressant activity.	Anticholinergic side effects, e.g. tachycardia, dry mouth, CVS side effects, e.g. postural hypotension, arrhythmias.	Do

Tricyclic and Tetracyclic Antidepressants

- These drugs have a long history of use in psychiatry, being introduced as early as in 1950s.
- Though drugs like SSRIs, bupropion, venlafaxine and mirtazapine has overshadowed its popularity, it still remains to be useful.
- They are used only when other anti-depressants are not effective.
- Act primarily by increasing NE and 5HT. Also act on H_1, $5HT_2$, α_1 and muscarinic receptors.
- Potent anticholinergic action causing dry mouth, blurred vision, constipation and urinary retention.

- Postural hypotension due to α_1 blockade, cardiac arrhythmias with ECG changes are seen.
- CNS effects like sedation, lack of concentration, lethargy, convulsions may occur. Weight gain creates a problem.
- Well absorbed orally.
- Long ½ life so once daily dosing.
- Metabolized by CYP2D6, CYP3A4 or CYP1A2 leading to drug interactions.
- Relatively narrow therapeutic window; plasma concentration monitoring may be necessary.
- *Pharmacokinetics*:
  - Oral absorption is complete.
  - First pass metabolism is significant.
  - Peak plasma concentration occurs in 2–8 hours.
  - t½ is about 10–70 hours.
  - Long t½ once daily dose.
  - Undergoes hepatic metabolism by CYP450 enzymes.
- *Mechanism of action:* Block the transporter site for NE or 5HT thereby increase their synaptic concentration.
  - Other effects, blocks muscarinic cholinergic receptors, H_1, α_1 and α_2 adrenoceptors.
- Pharmacological effects of TCA and Tetracyclic antidepressants are quite similar.
  - Sedation (serotonergic and anticholinergic, H_1 receptor antagonism).
  - Anticholinergic effects – dry mouth, constipation, urinary hesitancy, confusion and blurred vision.
  - Healing of peptic ulcer (H_2 blocking effect).
  - As TCAs undergo hepatic metabolism by cytochrome P450 enzymes, clinically relevant drug interactions can occur.
- *Indications for use*:
  - Major depression is the main indication. As they are likely to produce mania, hypomania than the newer antidepressants, they are C/I in treating depression associated with bipolar I and bipolar II disorders. Particularly used in refractory depression.
  - Panic disorder with Agarophobia – Imipramine is the most commonly used drug. Starting doses should be small to avoid side effects. Imipramine can also be used.

- Generalized anxiety disorder – Doxepin is used but Imipramine, can also be used.
- Obsessive compulsive disorder – Clomipramine is the drug of choice in depression associated with OCD.
- Chronic pain syndromes – Doxepin and Maprotiline are frequently used. Amitriptyline is used in chronic neuropathic pain and in the prophylaxis of migraine.
- Insomnia (chronic) – Amitriptyline, Doxepin.
- Headache – Amitriptyline, Imipramine, Doxepin.
- Bulimia – Imipramine, Desipramine.
- Childhood Enuresis – Impramine as adjunctive treatment
- Peptic ulcer disease – Doxepin.
- Other uses – Narcolepsy, nightmare disorder, post-traumatic stress disorder.

- To avoid toxicity blood level monitoring is done. Serum level of TCA is assessed from blood drawn 8–12 hours after patient's last dose when, consistent blood level is achieved (for TCA approximate 5–7 days therapy). Approximate therapeutic plasma concentration of antidepressants to be maintained are:
  - Amitriptyline – 100–250 mg/ml.
  - Desipramine – 150–300 mg/ml.
  - Doxepin – 120–250 mg/ml.
  - Imipramine – 150–300 mg/ml.
  - Maprotiline – 150–250 mg/ml.
  - Nortriptyline – 50–150 mg/ml.

  Overdose can result in death as Tricyclics have narrow margin of safety. Cause of death is usually arrhythmia.
- *Adverse effects*:
  - As TCAs have multivariate mechanism of actions, they produce myriad side effects– anticholinergic – dry mouth, blurred vision, constipation, urinary hesitancy, delirium.
  - *Cardiovascular:* Orthostatic hypotension, arrhythmia (tachycardia, prolonged QT intervals, depressed ST segment or flattened T waves in ECG). Palpitation and conduction slowing may be of concern. Hypertension can also occur.
  - *CNS effects*: Sedation, tremor, seizure (maprotiline), EPS (amoxapine), myoclonic twitches.

  - *Psychiatric effects:* Mania, hypomania, exacerbation of psychotic disorders.
  - *Allergic and hematological effects:* Rashes (Maprotiline), agranulocytosis, leukocytosis, leukopenia, eosinophilia.
  - *Hepatic effects:* Increase in level of SGOT, SGPT. Acute fulminant hepatitis can occur in 0.1%.
  - *Other effects:* Weight gain, sexual dysfunction (impotence, anorgasmia, ejaculatory disturbance), hyperprolactinemia, amenorrhea, gynecomastia, SIADH, nausea, vomiting and hepatitis.
- Drug interactions: Should not be combined with SSRI or MAOIs dangerous toxicity can occur.
  - TCAs decrease the action of indirectly acting sympathomimetics, antihypertensives like guanethidine, clonidine.
  - TCAs potentiate CNS depressants.
  - The secondary amine Tricyclics which selectively increase NE levels have actions similar to but lesser extent of adverse effects compared to the tertiary amine tricyclics. Adverse effects like sedation, anti-cholinergic action or weight gain are comparatively less.
  - One TCA, Amoxapine has additional dopamine receptor antagonistic action and has EPS adverse effects like tardive dyskinesia.
- Principles maintained to minimize side effect:
  - Start with minimum dose with moderate escalation if necessary.
  - For anticholinergic side effects – switch to Desipramine.
  - For orthostatic hypotension – nortriptyline is an alternative. Preferred in geriatric depression.
  - For weight gain, switch over to newer antidepressants.
  - Factors which tend to precipitate seizures like prolonged treatment (6 weeks) with high dose (225-400 mg/d) or rapid escalation of dose to be avoided during Maprotiline and Amoxapine therapy.
  - Tapering and stopping of medication if side effect like EPS appear before switching over to some other drug.
- *Contraindications*: Heart disease, conduction defects, hypertension, history of epilepsy or seizure, co-existent manic disorder.

Drug	*Receptor Affinity*						*Uptake Inhibition*	
	α_1	*Dose mg*	H_1	M_1	$5HT_1$	$5HT_2$	*5HT*	*NE*	*Dopamine*
Tertiary Tricyclics									
Amitriptyline	+++	150–300	++	+++	+/-	+/-	++	+	
Clomipramine	++	100–250	+	+	0	+	+++	++	
Imipramine	+	150–300	+	++	0	+/-	++	+	
Trimipramine	++		+++	++	0	+/-	0	0	
Doxepin	+++	150–300	+++	++	+/-	+/-	+	+	
Secondary Tricyclics									
Desipramine	+	150–300	+	+	0	+/-	+	+++	
Nortriptyline	+	50–150	+	+	+/-	+	+	++	
Protriptyline	+	15–60	+	+++	0	+	+	+++	
Tetracyclic Agents									
Amoxapine	++	150–400	+	+	+/-	+++	+	++	
Maprotiline	+	150–225	++	+	0	+/-	0	++	
Others									
Bupropion	0		0	0	0	0	0	+/-	+
Mirtazapine	0		+++	0	+	+	-	+	
Nefazodone	+		0	0	+	++	+	0/+	
Sertraline	0		0	0	0	0	+++	0	
Venlafaxine	0		0	0	0	0	++	+	

Adverse Effects Profile Compared

Adverse Effect	*Maximum*	*Minimum*
Orthostatic Hypotension	Imipramine, Amitriptyline, Clomipramine, Desipramine	Nortriptyline, Amoxapine, Doxepin, Maprotiline
Sedation	Amitriptyline, Clomipramine, Trimipramine	Protriptyline, Amoxapine, Desipramine
Seizures	Maprotiline and other Tricyclics	Desipramine, Nortriptyline, Protriptyline
Conduction Abnormalities	Trimipramine, Protriptyline, Amitriptyline, Clomipramine	Doxepin, Amoxapine
Anticholinergic Effects	Amitriptyline, Clomipramine, Trimipramine	Desipramine, Maprotiline

Drug Interactions of TCAs with following drugs:

- MAOIs → serotonin syndrome.
- SSRIs → increase in TCA level.
- Quinidine → increase in arrhythmia.
- Antipsychotics → increase in TCA level.
- Clonidine → antihypertensive action diminished.
- CNS depressants → increase in sedation, ataxia.

Discontinuation of TCAs

- Tapering of dose at the rate of 25–50 mg/2–3 days. Abrupt discontinuation may lead to rebound of cholinergic symptoms or rebound hypomania/mania.

Monoamine Oxidase Inhibitors

- Introduced in 1950s but not popular at present due to toxicity, food and drug interaction.
- Classified structurally as – Hydrazine derivatives – Phenelzine, Isocarboxazine, Non-hydrazine derivatives – Tranylcypromine, Selegiline, Moclobemide.
- Reversible inhibitors of MAOIs (RIMAs) like Moclobemide produce minimum food interactions.

- The hydrazine derivatives and tranylcypromine are irreversible and non-selective inhibitors of MAO-A and MAO-B, while the RIMAs are more selective.
- *Mechanism of action:* They act by inhibiting MAOs and increase the monoamine content. MAO-A is present in both dopamine and NE neurons, found in brain, gut, placenta and liver. MAO-A metabolises NE, 5HT and Dopamine. MAO-B is found in serotonergic and histaminergic neurons, found in brain, liver and platelets, metabolizes 5HT and Dopamine. 5HT and Dopamine are metabolized by both MAO-A and MAO-B. Phenelzine, Tranylcypromine → irreversible inhibitor of MAO-A.
- Moclobemide—selective and reversible inhibitor of MAO-A (displaced by Tyramine in food → cheese reaction).
- Selegiline at low dose – irreversible MAO-B inhibitor (at high dose non-selective MAO inhibitor).
- *Pharmacokinetics*:
  - Extensive first pass metabolism.
  - Well absorbed from GIT but poor BA.
  - Other routes of administration, e.g. transdermal and sublingual routes increase BA as well as decrease food-drug interactions.
  - Peak plasma concentration is reached in 2 hours.
  - t½ about 2–3 hours.
  - MAO enzymes are present in the outer membrane of mitochondria, degrading cytoplasmic, extra-neuronal monoamine neurotransmitters.
- *Therapeutic indications*:
  - Depression refractory to TCAs.
  - Anxious depression → Phenelzine.
  - Atypical depressive syndrome → Phenelzine, Moclobemide.
  - Social phobia.
- *Adverse effects*:
  - Most common is dizziness.
  - Orthostatic hypotension.
  - Hypertensive crisis (food/drug interaction).
  - Sedation/insomnia during night.
  - Weight gain.
  - Constipation, dry mouth, urinary hesitancy.
  - Muscle cramps, myoclonic twitches.
- Greatest adverse effect is food/drug interaction which may lead to hypertensive crisis.
  - CVA.

- serotonin syndrome → hyperpyrexia, mental status alteration, delirium, which can lead to coma and death.

- These are now rarely used due to their major food and drug interactions and toxicities.
- Irreversible inhibition of MAO-A and MAO-B, leads to increase of endogenous monoamines like 5HT, NA and dopamine resulting in various adverse effects and exogenous monoamines like tyramine in food.
- Interacts with other antidepressants like SSRI, SNRI, and TCAs to cause serotonin syndrome.

  Excess stimulation of 5HT receptors result in following effects:
  CNS – delirium, coma, tremor.
  CVS – tachycardia, hypertension, diaphoresis.
  Somatic – hyperreflexia, myoclonus.

  All serotonergic drugs should be withdrawn for at least 2 weeks before starting a MAOI; for fluoxetine the withdrawal period should be 4–5 weeks. Similarly MAOIs should be discontinued for at least 2 weeks before starting any serotonergic agent.
- When MAO-I are given in addition to tyramine in diet; patient may suffer from malignant hypertension or myocardial infarction or stroke; also known as 'cheese reaction'. So patients on MAOIs should avoid foods like aged cheeses, tap beer, soy products, dried sausages and require a low-tyramine diet.
- MAOIs which inhibit both MAO-A and MAO-B are tranylcypromine, phenelzine and isocarboxazid. MAO-A inhibitor moclobemide and MAO-B inhibitor selegiline are rather used.
- To avoid high first pass metabolism, selegiline is available as transdermal patch or sublingual forms to increase BA.

Precautions to be maintained during anesthesia:

- There are chances of dangerous drug interactions in patients on MAO inhibitors. Sympathomimetic drugs may precipitate potentially dangerous hypertensive crises.
- Opioid drugs like Pethidine, Tramadol and Dextromethorphan, which have serotonergic properties, may precipitate serotonin syndrome.
- MAO inhibitors can inhibit hepatic microsomal enzymes and increase the serum concentration of opioids, enhancing chances of toxicity.
- Pancuronium should be avoided in these patients as it releases stored NA.

- Phenelzine can decrease plasma cholinesterase level, thereby increasing the duration of action of succinylcholine.
- Use of cocaine should be prevented, other LAs are safe.
- Among the opioids, Morphine can be safely used,though Fentanyl, Alfentanil, Sufentanil or Remifentanil are not contraindicated.
- Of the vasopressor agents, Felypressin is used instead of Adrenaline.
- If patient is on antipsychotic drug, it should not be abruptly withdrawn.
- Antipsychotic drugs may potentiate the sedative and hypotensive actions of anesthetic agents.
- Lithium potentiates both depolarizing and non-depolarizing muscle relaxants.
- NSAIDs should preferably be not used in patients on Lithium.
- Foods to be avoided:
  - Aged cheese.
  - Beer, red wine.
  - Dry sausage, smoked fish, liver.
  - Fava/Italian green beans.
  - Alcohol, yoghurt, banana, soyasauce (in excess quantity).
- If a patient develops high rise in BP with violent headache
  - Phentolamine IV can be used.
  - Nifedipine 10 mg/hr 1–2 doses.
- Monitoring of BP is advisable during first 6 weeks of initiation of therapy.
- Transition from TCA to MAOI requires 10–14 days drug free interval.
- Withdrawal of MAO should be done in tapering dose and it takes two weeks for the enzymes to regenerate. During this period precaution to be taken for food and drug.
- Some newer antidepressants:
  - Agomelatin – $5HT_2$ antagonist and melatonin agonist. Used for antidepressant and anxiolytic properties.
  - Dose – 25–50 mg/day.
  - Gepirone – Potent $5HT_{1A}$ agonist. Used in generalized anxiety disorder and major depression.

Newer Antidepressants

- Noradrenergic Reuptake Inhibitors (NARIs)
  - Reboxetine.
  - Atomoxetine.

- Melatonin agonist and $5HT_{2C}$ antagonist – Agomelatine.
- Novel Antidepressants – Triple Reuptake Inhibitors – Inhibit reuptake of NE, 5HT and Dopamine – Tesofensive.
- Selective partial receptor agonist and reuptake inhibitor (SPARI)-Vilazodone.

Atomoxetine

- FDA approved for treatment of ADHD in children and adults.
- Carries the blackbox warning of increased rate of suicidality in this age group of patients.
- Average dose is 40-100 mg/day/1.2 mg/kg body weight.
- Improves attention more than hyperactivity.
- Adverse effects – loss of appetite, GI upset.

Agomelatine

- Novel antidepressant.
- $5HT_{2C}$ blocking results in both antidepressant and anti-anxiety effect.
- Melatonin MT_1 and MT_2 receptor agonistic action induces sleep.
- Advantage – Less sexual side effect and less daytime sedation, no evidence of weight gain.
- Adverse effect – Headache, nasopharynx, GI upset.
- Dose – 25–50 mg/day.

Vilazodone

First member of the group, selective serotonin receptor agonist and reuptake inhibitor.

- Blocks the serotonin reuptake by inhibiting the serotonin transporter and increases serotonergic transmission.
- Partial agonistic action at the presynaptic $5HT_{1A}$ receptor enhances 5HT activity and decreases depressive symptoms while partial agonistic action at the postsynaptic serotonin 1A receptors may decrease the sexual dysfunction adverse effect of normal SSRIs.
- *Advantages*: Minimum weight gain and sexual dysfunction as adverse effects. Antidepressant of choice in depression associated with anxiety.

- Plasma t½ life of about 25 hours, metabolized by CYP 3A4.
- *Indications*:
  - Treatment resistant depression.
  - Treatment resistant OCD.
  - Anxiety disorders.
- *Dose:* 50–80 mg/day.
- *Adverse effects*:
  GI-nausea, vomiting, CNS- insomnia, dizziness, rarely, bleeding and hyponatremia.
- Contraindications: History of seizure, BPD, children, adolescents.

CLINICAL PEARLS

- As TCAs and Tetracyclic antidepressants are associated with weight gain, it is advisable to take baseline BMI before initiation of therapy.
- Amitriptyline is effective in primary insomnia.
- Underweight patients on Amitriptyline are more susceptible to cardiovascular adverse effects.
- Amoxapine has faster onset of action compared to other antidepressants and is structurally and pharmacologically related to antipsychotic Loxapine.
- Bupropion may be added to SSRIs to reverse SSRI induced sexual dysfunction; used along with atypical antipsychotics/mood stabilizers in BPD.
- Clomipramine is the only TCA which is effective in OCD but produces fatal drug interactions with MAOIs.
- Fluoxetine along with Olanzapine produce excellent result in BPD.
- Fluoxetine or Sertraline may be used as first line therapy in atypical depression.
- Fluvoxamine additionally acts on sigma receptors, thereby is effective in anxiety and insomnia associated with depression.
- Withdrawal symptoms are more likely with Paroxetine therapy compared to other SSRIs.
- Vilazodone acting on $5HT_{1A}$ receptors have early onset of action and less adverse effects compared to other SSRIs.
- Doxepin is the only TCA available in topical formulation to be used in various neurodermatological syndromes.

Chapter

7 Antipsychotics

1. First Generation/Typical or Conventional Antipsychotics:
   Chlorpromazine — Haloperidol
   Trifluopromazine — Trifluperidol
   Thioridazine — Pimozide
   Trifluoperazine — Loxapine
   Fluphenazine
2. Second Generation/Atypical Antipsychotics:
   Clozapine — Aripiprazole
   Risperidone — Ziprasonidone
   Quetiapine — Amisulpride
   Olanzapine — Zotepine
3. Long Acting depot antipsychotics:
   Flupentixol decanoate
   Fluphenazine decanoate
   Haloperidol decanoate
   Olanzapine Pamoate
   Risperidone Consta
   Zuclopenthixol decanoate.

Pharmacokinetics

- Well absorbed from GIT, absorption may be affected if antacids/anticholinergics are co-administered.
- Low potency antipsychotics like chlorpromazine, thioridazone have a wide dosing range while highly potent antipsychotics like risperidone, olanzapine have a narrow dose range and needs titration of dose monitoring.
- Highly lipid soluble.
- Highly plasma protein bound, mainly to albumin.
- Metabolized primarily in liver by CYP P450 and undergoes glucuronidation before being excreted in urine.
- Antipsychotics are slowly released from lipid rich storage sites and metabolites can be detected in urine even after 3 months of discontinuation of the drug.

Mechanism of Action

- D_2 receptor antagonism is the main mechanism of action of most antipsychotics.
- Atypical antipsychotics have a greater $5HT_2$ antagonism than D_2 receptor antagonism. They also act selectively at D_4 receptors which are sparse in basal ganglia.
- Aripiprazole is unique by being partial agonist at D_2 (both are pre- and post-synaptic) partial agonist at $5HT_{1A}$ and antagonist at $5HT_{2A}$ receptors. Partial dopamine agonists action may be agonistic/antagonistic depending on the degree of receptor stimulation/concentration of endogenous ligand. Weaker D_2 blockade causes less EPS side effects.

Indications

- Used in treatment of various psychotic disorders including schizophrenia, mania with psychotic symptoms, dementia with delusions, agitation or delusional disorders, delirium secondary to medical conditions.
- Short-term therapy is employed in dementia or delirium with psychotic symptoms. Oral dissolving tablets of risperidone, aripiprazole and olanzapine or liquid concentrate are advisable.
- Atypical antipsychotics except clozapine, iloperidone are used in acute mania, in rapidly titrating doses to maximum high dose. Combination of antipsychotic with a mood stabilizer like lithium or valproic acid is often necessary for a further period after control of symptoms.
- Clozapine is useful in refractory schizophrenia.
- Major depression associated with psychotic features is treated with atypical antipsychotics. Aripiprazole is FDA approved for adjunct therapy with antidepressants.
- Schizophrenia: Newer atypical antipsychotics are preferred to typical antipsychotics for better adverse effect profile. Long-term treatment is often necessary.
- Acute symptoms respond within hours of therapy but therapy for weeks is necessary for maximum drug response. Long acting depot injectables are available for long-term therapy in schizophrenia, specially Fluphenazine, Haloperidol, Risperidone decanoate and Paliperidone Palmitate.
- Alcoholic hallucinations, Huntington's Disease, Gilles de la Tourette's syndrome.

Principles of Therapy

- Dose of antipsychotic is individualized by titration according to response to symptoms.
- Starting dose should be kept to minimum.
- Combination of two antipsychotics is usually of no advantage, can only be added at times to control acute violent symptoms as injectables.
- Quetiapine is the preferred drug when given to a depressed psychotic.
- Chronic schizophrenia patients need at least 2–4 months therapy for maximum therapeutic response.
- Delirium is the only indication when Haloperidol is routinely used in elderly. In conditions other than delirium, atypical antipsychotics are the preferred drugs in elderly but clozapine is avoided for agranulocytosis as adverse effect. Cautious use of antipsychotics in elderly has been FDA recommended.

Associated Medical Conditions

	Condition	*Drug of Choice*	*Drugs to be Avoided*
1.	Diabetes	Aripiprazole	Clozapine, Olanzapine
2.	Hyperlipidemia	Aripiprazole	Clozapine, Olanzapine
3.	Orthostatic hypotension	Aripiprazole	Clozapine, Quetiapine, Risperidone
4.	Weight gain/ Obese	Aripiprazole, Molindone	Clozapine, Olanzapine
5.	Glaucoma	Aripiprazole, Risperidone, Quetiapine	Clozapine, Thioridazine
6.	Prostate hypertrophy	Do	Clozapine, Olanzapine, Thioridazine
7.	QTc prolongation	Olanzapine	Thioridazine, Ziprasonidone
8.	Parkinsonism	Low dose Clozapine, Quetiapine	Haloperidol
9.	Dryness of eyes or dryness of mouth	Aripiprazole, Risperidone, Quetiapine	Clozapine, Thioridazine
10.	Hypomania/Mood	Quetiapine, Olanzapine	

- In hepatic insufficiency, dose of antipsychotic should be reduced.
- After starting antipsychotic therapy patient should be assessed within 1–2 weeks.
- After a dose change, patient should be advised to come for follow up within 1 month.
- After dose titration has been achieved, patient should be monitored every 2–3 months.
- For therapeutic dose monitoring, only drugs with few active metabolites can be assessed usefully, e.g. clozapine, haloperidol, fluphenazine, thioridazine, perphenazine.
- Treatment resistance is defined as non-response to two antipsychotic therapy in adequate dosage.
- Adjunctive therapy with mood stabilizers should be used to augment partial response.

Use in other conditions

1. Bipolar mood disorders: Combination of antipsychotic like Olanzapine with a mood stabilizer is more effective than mood stabilizers used alone.
   Schizoaffective disorder/Resistance bipolar disorder: Clozapine has been found to be effective.
   Acute mania: Olanzapine, Ziprosonidone, Aripiprazole, Quetiapine, Risperidone have FDA approval for use.
   Bipolar depressive disorder: Olanzapine is often used in combination with Fluoxetine.
2. Unipolar depression: Any antidepressant with antipsychotic works well in psychotic depression.
3. Generalized anxiety disorder: Quetiapine is a good choice. It is also a non-habit forming alternative to Benzodiazepine.
4. Personality disorders: In borderline and schizotypical personality disorders, combinations like Paroxetine with Risperidone or Fluoxetine and Olanzapine are often effective.

First Generation Antipsychotics

Drug	*Adverse Effects*	*Dose mg/day*
Chlorpromazine	EPS, sedation, hypotension	100-800
Triflupromazine	EPS, sedation, hypotension	50-200
Thioridazine	Sedation, hypotension	100-400
Trifluoperazine	EPS, sedation, hypotension	2-20
Fluphenazine	EPS, mild sedation, hypotension	1-10
Haloperidol	EPS, Similar adverse effects	2-20
Trifluperidol	EPS	1-8
Flupenthixol	EPS	3-15
Pimozide	EPS	2-6
Loxapine	EPS, hypotension	20-50

Uses of Typical (D_2 antagonist) Antipsychotics

1. Positive symptoms schizophrenia.
2. Tourette's disorder (pimozide).
3. Mania (chlorpromazine).
4. Drug-induced psychosis.
5. Vomiting, hiccups, agitation.

Second Generation/Atypical/Dopamine Serotonin Antagonist Antipsychotics

Sl. No.	*Drug*	*Indication*	*Dosage*	*Adverse Effects*	*Special Remarks*
1.	Clozapine	Refractory schizophrenia.	12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg tab, 25–200 mg/day OD.	Sedation, weight gain, hyperlipidemia, diabetes, agranulocytosis, orthostatic hypotension, hypersalivation.	Relative selectively to D_4 receptor, additional $5HT_2$ and α-receptor block, WBC count monitoring to be done.
2.	Risperidone	Schizophrenia, acute mania, schizoaffective disorder.	2–6 mg/day.	Hyperprolactinemia, increased risk of stroke in elderly, orthostatic hypotension.	Combined D_2 and $5HT_2$ blockade also α_1, α_2, H_1 receptor block, BP increase when given along with SSRI.
3.	Olanzapine	Positive and negative schizophrenia, acute mania, bipolar disorder, agitation.	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg tablets. 5–20 mg/day OD. Injection available.	Dry mouth, constipation, increase in prolactin, hyperglycemia, weight gain, epileptogenic, postural hypotension.	Blocks D_2, $5HT_2$, α_1, α_2, muscarinic and H_1 receptors also D_1, D_3 and D_4. Most commonly used and most expensive.

Contd...

Sl. No.	Drug	Indication	Dosage	Adverse Effects	Special Remarks
4.	Quetiapine	Acute mania, bipolar depression, negative symtoms of schizophrenia	50–100 mg/day → 400–800 mg/day	Sedation, weight gain, postural hypotension, hyperglycemia	Blocks $5HT_{1A}$, $5HT_2$, D_2, α_1, α_2, H_1R.
5.	Aripiprazole	Schizophrenia, mania, bipolar disorders, adolescents with schizophrenia	10 mg, 30 mg, 5 mg tablet, 5–10 mg/day	Insomnia may occur, nausea, dyspepsia, constipation. Other side effects are minimum	Partial agonist at D_2, $5HT_{1A}$ but antagonist at $5HT_2R$, long acting (t½ 3 days).
6.	Ziprasonidone	Schizophrenia, mania, agitation in psychotic patients, bipolar manic patients	60–80 mg BD → 120–160 mg, BD/day. Injection available	Postural hypotension, mild sedation, weight gain, hyperglycemia, nausea, vomiting, increase in QTc → cardiac arrhythmias	Blocks D_2, $5HT_{2A/2C}$, α_1, H_1, $5HT_{1D}$, agonistic at $5HT_{1A}$. Blocks NE reuptake, additional antidepressant and anxiolytic property.

Antipsychotic Depot Preparations

1. Flupentixol decanoate: 20–100 mg IM every 2–4 weeks.
2. Fluphenazine decanoate: 12.5–100 mg IM every 2–4 weeks.
3. Haloperidol decanoate: 25–250 mg IM every 4 weeks.

4. Olanzapine Pamoate: 150–300 mg IM every 2 weeks/40–50 mg every 4 weeks.
5. Risperidone Consta: 25–75 mg IM every 2 weeks.
6. Zuclopenthixol decanoate: 200–400 mg IM every 2–4 weeks.

As adherence to oral medication is often difficult in many psychotic patients including schizophrenia, injectable once or twice a month is of convenience in maintenance.

CLINICAL PEARLS

- Conventional antipsychotics can only be added to atypical antipsychotics in treatment failure cases.
- ECG, cardiac evaluation, baseline liver function tests, fasting glucose, fasting lipid should be done before initiation of therapy and monitored at 3 monthly intervals during therapy; BMI should also be monitored.
- Haloperidol can be used along with Lorazepam in treatment of delirium.
- In treatment resistant schizophrenia, one depot antipsychotic is often combined with one oral antipsychotic.
- Pimozide can increase QTc interval and potentially cause arrhythmia or sudden death, specially when administered along with microsomal enzyme inhibitors like erythromycin, ketoconazole or protease inhibitors.
- Quetiapine can increase the risk of diabetes and dyslipidemia but is useful in patients with Parkinsonism or Lewy body dementia needing antipsychoic therapy.
- Risperidone is preferred in behavioral therapy of children and in agitated, aggressive elderly patients with dementia.
- The adverse effect of prolonging QTc interval leading to cardiac arrhythmia and sudden death associated with thioridazine, outweighs its beneficial effects.
- Ziprasonidone can cause weight loss and decrease blood triglyceride level in obese patients; a short acting IM preparation is also available.

Chapter

8 Mood Stabilizers

The term "Mood stabilizers" was first introduced in reference to lithium salts when it was found effective not only to alleviate mania but also prevented both manic and depressive episodes. Now various drugs including some anti-epileptics and second generation anti-psychotics have been found to be effective in bipolar mood disorders.

MOOD STABILIZERS

1. Lithium Carbonate.
2. Sodium Valproate.
3. Carbamazepine.
4. Lamotrigine.
5. Atypical antipsychotics – Olanzapine, Risperidone, Quetiapine, Aripiprazole.

Combination of atypical antipsychotics with valproate or lithium has been found to be very effective in acute phases as well as for maintenance therapy. Anticonvulsants like Gabapentin, Oxacarbazepine, Topiramate and Tiagabine have also been found to be useful.

- Advantages of second generation antipsychotics in treatment of acute mania
  - rapid onset of action compared to lithium/others.
  - less EPS incidence.
- As the onset of antimanic effects of lithium, valproate or carbamazepine takes 1 week/longer it is advisable to start therapy with second generation antipsychotics (SGA).
- Patients who are unresponsive to a therapeutic dose of SGA for 3–7 days are to be treated with add-on mood stabilizers like lithium or valproate.
- Benzodiazepines are also a reasonable adjunct to SGA in acute mania.

- For bipolar depression, combination of Fluoxetine and Olanzapine is well approved. The second drug of choice is Quetiapine which is the only monotherapy for bipolar depression at present.
- Maintenance therapy: Lithium was the first maintenance medication approved for bipolar disorder. Lamotrigine is the second drug of choice. Other drugs approved for maintenance are Olanzapine, Divalproex and Carbamazepine.

Lithium

- Usually lithium carbonate and occasionally lithium citrate is used in acute manic episodes as well as for maintenance therapy of bipolar disorder.
- *Mechanism of action*: Proposals regarding mechanism of action are:
  - Lithium replaces Na^+ in the body and becomes equally distributed both intracellularly and extracellularly. This may affect ionic fluxes across brain cells.
  - May decrease presynaptic release of NA and DA in brain without affecting 5HT release.
  - Inhibits hydrolysis of inositol-I-phosphate by inositol monophosphate, hence the source of IP_3 and DAG is reduced in neurons.
- *Pharmacokinetics*:
  - Well absorbed orally.
  - Not protein bound or metabolized.
  - Excretion via kidney is rapid for first 10–12 hours followed by a slower phase of excretion lasting for several days.
  - Plasma therapeutic concentration is 0.5 to 0.8 mEq/litre.
  - Toxicity occurs when plasma concentration is more than 1.5 mEq/litre.
  - Lithium is also excreted through sweat, saliva and breast milk.
- *Adverse effects*:
  GI: Nausea,vomiting, diarrhea.
  CNS: Tremor, ataxia, nystagmus, mental confusion, slurred speech, motor incoordination.
  In acute intoxication: Severe vomiting, diarrhea, albuminuria, delirium, convulsion, drowsiness, coma, hypotension, cardiac arrhythmias.
  Chronic toxicity: Weight gain, renal diabetes, insipidus, goiter with/without hypothyroidism, dermatitis.

- *Preparations*:
  - Lithium carbonate – 300 mg capsules/scored tablets, sustained release preparations are available. 300 mg of lithium carbonate equivalent to 8 mEq.
  - Lithium citrate – SR tablets and liquid preparations (1 tsf 300 mg equivalent to 8 mEq).

Other Mood Stabilizers

	Serum Therapeutic Level	*Dosage*	*Side Effects*
Valproate	50–125 µg/ml	15–60 mg/kg/day	Sedation, tremor, ataxia, increase in liver enzymes, pancreatitis, rash, alopecia, thrombocytopenia.
Carbamazepine	6–10 µg/ml	200–1600 mg/day	Sedation, dizziness, ataxia, increase in liver enzymes, SIADH, arrhythmia, thrombocytopenia.
Lamotrigine	NA	50–200 mg/day	Somnolence, ataxia, nausea, vomiting, rash, acne, vaginitis, UTI.
Gabapentin	NA	900–3600 mg/day	Somnolence, dizziness, ataxia, dyspepsia, leucopenia.
Oxcarbazepine	NA	600–2400 mg/day	Increase in liver enzymes, hyponatremia.

Formulations

1. Lithium Carbonate: Capsule 150/300/600 mg; CR tab 300 mg; SR tab 450 mg.
2. Lithium Citrate: Syrup 8 mEq/ml (480 ml bottle).
3. Valproic Acid: Capsule 250 mg; syrup 250 mg/5 ml (480 ml bottle).
4. Valproate Sodium: Injection 100 mg/ml (5 ml/vial).
5. Carbamazepine: Tab 200 mg; chewable tab 100/200 mg; suspension 100 mg/5 ml (450 ml bottle).
6. Lamotrigine: Tab 25/100/150/200 mg, chewable tab 2/5/25 mg.

7. Gabapentin: Tab 100/300/400/600/800 mg; cap 100/300/400 mg; suspension 250 mg/5 ml.
8. Oxcarbazepine: Tab 150/300/600 mg; suspension 300 mg/5 ml.

CLINICAL PEARLS

- Valproate is the first line treatment of choice in cases of mixed type of bipolar disorder or rapid cycling bipolar disorder.
- Valproate is also used in treating agitation and aggression associated with dementia, schizophrenia, bipolar disorder, brain injury and personality disorder.
- Pregabalin is the treatment of choice in diabetic or peripheral neuropathy and fibromyalgia; is more potent and better tolerated than gabapentin.
- Lamotrigine is the first line therapy in bipolar depression; also best tolerated mood stabilizer with minimum weight gain or sedation as adverse effect.
- Topiramate is used to treat psychotropic drug-induced weight gain.

Chapter

9 Anxiolytics

- Benzodiazepines are the most frequently prescribed anxiolytic agents.
- Buspirone a $5HT_{1A}$ serotonin agonist with some dopaminergic effects is also a useful anti-anxiety agent.
- Anticonvulsants like Gabapentin and Pregabalin or antidepressants are often common adjuncts in treating some anxiety states.

BENZODIAZEPINES

Indications of Use of Benzodiazepines

- Generalized anxiety disorders.
- Panic disorders (Alprazolam).
- Muscle relaxation for increased muscle tension.
- Myoclonic epilepsy (Clonazepam).
- Febrile convulsion/Drug-induced convulsion/Status epilepticus (Diazepam).
- Insomnia.
- Anxiety associated with depression (Alprazolam).
- Acutely agitated psychotic patients (IM Lorazepam).

Withdrawal

As a rule, reduction in dose should be made at a maximum rate of 10% per day. Many patients need much slower tapering specially the elderly. Withdrawal symptoms have been observed if drugs are withdrawn abruptly in patients on prolonged drug therapy, e.g. for 7 or 8 months.

Symptoms on Withdrawal

- Anxiety, jitteriness.
- Palpitations, sweating, nausea.

- Confusion, increase in sensitivity to light and sound.
- Rebound insomnia, rarely precipitation of seizures.

Other Anti-anxiety Drugs

β-*Blocker Propranolol*

Indications of use

- Anxiety associated with palpitations, tremor.
- Tremors secondary to lithium carbonate use.
- Akathisia in patients on antipsychotics.
- Generalized anxiety.
- Anxiety associated with public performance.

Dosage:

1. For lithium-induced tremor/familial tremor 10 mg twice daily is administered. Dose may be increased to 30–120 mg/day. Major adverse effect is lethargy.
2. For socially phobic situations 10–20 mg once/twice before a performance, can be used to block stage fright.

Other adverse effects – Bradycardia, hypotension, fatigue, altered sensorium, bronchospasm.

BUSPIRONE

- Non-benzodiazepine, non-sedative anxiolytic.
- *Mechanism of action:* Partial agonist at $5HT_{1A}$ receptor, weak D_2 blocker.
- Does not produce tolerance or physical dependence and is devoid of muscle relaxant or anticonvulsant property.
- Rapidly absorbed after oral administration, undergoes high first pass metabolism, bioavailability is less than 5%.
- Onset of action of full anti-anxiety effect takes 2–4 weeks.
- Dose: 5 mg BD, may be increased to 30–60 mg/day.

Indications for Use

- Generalized anxiety disorder.
- Social phobia.
- Mixed anxiety with depression.
- Anxiety associated with substance abuse.
- Medically ill elderly patients and AIDS patients with anxiety.

Adverse Effects

- Nausea, headache, dizziness.
- May exacerbate psychosis in patients with schizoaffective disorder.

Otherwise well-tolerated drug, with minimum effect on discontinuation.

Advantages

Non-sedating, does not impair motor coordination, no physical dependence or withdrawal symptoms, safe in elderly and alcoholics.

Chapter

10 Centrally Acting Analgesics-Opioids

- Opiate → compounds structurally related to opium ('opos' → Greek word means juice).
- Natural opiates derived from poppy (somniferum) papaver. Natural plant alkaloids: (i) morphine, (ii) codeine, (iii) thebaine.
- Endogenous opioids are naturally occurring ligands for opioid receptor.
- Endorphin or endogenous opioid peptides, e.g. β endorphin.
- Narcotic is a drug which induces narcosis or sleep (word derived from Greek word narkotikos meaning stupor).
- Opium contains more than 20 distinct alkaloids.

Endogenous Opioid System

- The endogenous opioid peptides are derived from a distinct large precursor protein, e.g.

Encephalin	Preproopiomelanocortin
Endorphin	Preproenkephalin
Dynorphin	Preprodynorphin

- Actions of opioid ligands:

Sl. No.	*Agonists*	*Vide Opioid Receptors*		
		μ	δ	κ
1.	Etorphine	+++	+++	+++
2.	Fentanyl	+++		
3.	Levorphanol	+++		
4.	Methadone	+++		
5.	Morphine	+++		+
6.	Hydromorphone	+++		+
7.	Sufentanil	+++	+	+

Contd...

Sl. No.	Agonists	Vide Opioid Receptors		
		μ	δ	κ
8.	Met-enkephalin and Leu-enkephalin	++		+++
9.	β-Endorphin	+++	+++	
10.	Dynorphin A	++		+++

- The POMC sequence contains a variety of non-opioid peptides including ACTH, MSH (α), β lipotropin; all are generated by proteolytic cleavage of POMC.
- The major opioid peptide derived from further cleavage of β-lipotropin is the potent opioid agonist, β-endorphin.
- The anatomical distribution of POMC producing cells is relatively limited in the CNS:
  - arcuate nucleus of hypothalamus.
  - nucleus tractus solitarius.
- Proenkephalin contains multiple copies of met-enkephalin and single copy of leu-enkephalin.
- Prodynorphin contains three peptides, dynorphin A, dynorphin B and neoendorphin.
- Recently a family of peptides named endomorphin namely, endomorphin 1, endomorphin 2, have been identified with selectivity towards μ opioid receptor.

Opioid Receptors

- The three opioid receptors δ, μ, and κ belong to the rhodopsin family of GPCRs and share extensive homologies.
- Their effects on CNS function depend on the density and diverse distribution of receptors in the brain and spinal cord.
- These receptors are expressed in a variety of peripheral sites, e.g. blood vessels, heart, lung, airways, gut, inflammatory and circulating cells.
- The classical opioid receptors has an endogenous ligand, nociceptin/orphanin (FQ:N/OFQ) whose binding sites have been found in CNS – cortical regions, ventral forebrain, hippocampus, brainstem and spinal cord; in peripheral cells-basophils, endothelial cells, macrophages.

- Opioid receptor activation results in following intracellular events:
  - inhibition of adenylyl cyclase activity.
  - reduced opening of voltage gated Ca^{2+} channels.
  - stimulation of k^{+} current through several channels.
  - activation of PKC and PLCβ.
- Functional consequences of acute and chronic opiate receptor activation:
  - desensitization.
  - tolerance: sustained administration of an opiate (days to weeks) leads to progressive loss of drug effect.
  - Phenomenon can be manifested at intracellular and at organ level.
- Tolerance is time dependent; occurring over short term period.
- Reversible over time.
- Tolerance develops in variable rates:
  - little/no tolerance → pupillary miosis.
  - moderate tolerance → constipation emesis, analgesia, sedation.
  - rapid tolerance → euphoria.
- Dependence: Dependence represents a state of adaptation manifested by withdrawal symptoms produced by cessation of drug exposure; manifested by agitation, hyperalgesia, hyperthermia, hypertension, diarrhea, pupillary dilation, dysphoria, anxiety, depression.
- Addiction: Behavioral pattern characterized by compulsive use of a drug and overwhelming involvement with its procurement and use.
- Mechanism: Acute desensitization, receptor internalization, endocytosis, sequestration of receptors.

Effects

1. *Analgesia*: Analgesia produced by morphine like drugs is associated with drowsiness, changes in mood, mental clouding. Some may experience euphoria. Dull pain is relieved more effectively than sharp intermittent pain. Inflammatory pain often referred to as nociceptive pain. Neuropathic pain responds less well to opioid analgesics.
   Mechanism:
   i. Block release of GABA from PAG systems (periaqueductal gray matter).
   ii. Action of PAG outflow.

iii. Activation of forebrain and spinal cord.
iv. Monoamines provide sensory input to higher centers and mood (NE and 5HT).
Opiate binding to receptor is highly expressed in the superficial spinal dorsal horn (substantia gelatinosa).
v. Presynaptically opioids block opening of Ca^{+2} channel and post-synaptically enhances opening of K^{+} channels leading to hyperpolarization.
vi. Prevent release of excitatory neurotransmitters from C fibers.
Direct application of opiates to a peripheral nerve produce a local anesthetic like action at high concentration but it is not reversible with Naloxone.
Euphoria, tranquility and mood alter by opiates is due to the role of mesocorticolimbic dopamine system.

2. *Respiration*: Respiratory depression rarely occurs with standard analgesic dose. Opioids should be used with caution in patients with asthma, COPD, cor pulmonale, hypoxia, decreased respiratory drive.
Normal rate and rhythm of respiration is controlled by respiratory center in ventrolateral medulla; PO_2 is measured by chemosensors in carotid and aortic bodies and CO_2 is measured by chemosensors in brainstem. Morphine like opioids depress respiration through MOR and DOR receptors with changes in respiratory pattern; opiates depress the chemosensory receptors of brainstem; thus hypoxic stimulation too is depressed. In addition:
– Opioids ↑ chest wall rigidity and ↓ upper airway patency.
– Factors exacerbating opiate-induced respiratory depression:
i. Medications – General anesthetics, tranquilizer, alcohol, sedative hypnotics.
ii. Sleep – Normal sleep causes ↓ sensitivity of medullary center to CO_2; depressant action of morphine acts as additive factor.
iii. Age – Newborns and elderly are at greater risk of depression.
iv. Disease – Opiates causes greater depressant action in patients with chronic cardiorespiratory/renal disease.
v. COPD - ↑ depression is seen in patients with COPD/sleep apnea if opiates are administered.

3. *Sedation*: Drowsiness, cognitive impairment, increased incidence in dementia, encephalopathies, brain tumors and depressant medications.
   Maximal respiratory depression occur within 5–10 min of IV morphine, 30–90 min after IM/SC. Rapid depressant effects occur with lipid soluble agents.

Codeine

- Methyl-morphine; converted in the body to morphine.
- ⅒th analgesic as morphine.
- Partial agonist at μ opioid receptor.
- More selective cough suppressant.
- Orally absorbed; t½ life 3–4 hours.
- Constipation occurs.
- Abuse liability is low, no dependence liability.
- Effective only in mild pain, used to suppress cough.

Pethidine/Meperidine

Piperidine derivative:

- Synthesized as atropine substitute, interacts with opioid receptors; actions blocked by naloxone.
- Analgesic ⅒th that of morphine, more than codeine.
- Quick onset of action on IM inj; duration 2–3 hours.
- Sedative, euphoriant, respiratory depressant, abuse liability is present.
- Tachycardia (due to anticholinergic activity), mydriasis.
- Less histamine release.
- Administered orally/IM, active metabolite.
- Completely metabolized in liver, excreted in urine.
- Overdose causes excitatory effects.
- Used as analgesic, as pre-anesthetic medication.

Fentanyl

- Pethidine congener: highly potent analgesic.
- 80–100 times > potent than morphine.
- Respiratory depression occurs but CVS side effect minimum.
- Does not release histamine.

- Highly lipid soluble, enters brain, t½ <4 hours.
- Transdermal patch available.
- Used in chronic pain, in anesthesia.

Methadone

- Synthetic opioid with long half life.
- Blocks both NMDA receptors and monoamine reuptake transporters; hence used to treat severe pain.
- Superior analgesic at 10–20% of morphine equivalent dose.
- Has analgesic, respiratory depression, constipation, nausea, vomiting, and anti-tussive actions similar to morphine.
- Administered orally or IM.
- t½ 24–36 hours; highly protein bound (90%).
- Slow persistent action, sedation is less.
- Used as analgesic or to remove opioid dependence in addicts.
- Abuse liability is low, slow tolerance development, minimum withdrawal symptoms.
- *Dose*: 2.5–10 mg oral/IM.

Tramadol

- Centrally acting analgesic.
- Affinity for opioid receptors low; partially antagonised by naloxone.
- Inhibits reuptake of NA, 5HT and activates monoaminergic inhibition of pain at spinal level.
- Metabolite of antipsychotic Trazodone.
- Used in mild-moderate pain, chronic pain including cancer pain but not effective in severe pain.
- Well tolerated minimum hemodynamic changes; minimum abuse liability.

Uses of Morphine and Congeners

- As analgesic: Traumatic, visceral, ischemic, postoperative, burn, cancer pain.
- Routes-Epidural, intrathecal, transdermal.
- Preanesthetic medication.
- Balanced anesthesia.
- Relief of anxiety and apprehension.
- Acute LVF: Morphine.

- Cough: Codeine, dextromethorphan, levopropoxyphene.
- Diarrhea: Diphenoxylate, loperamide.
- Shivering: Pethidine, tramadol.

Agonist-Antagonist

Pentazocine

- Weak μ antagonistic and marked k agonistic actions; it is a benzomorphan.
- Analgesia primarily spinal; 30 mg equivalent to 10 mg of morphine.
- Sedation, respiratory depression ⅓ - ½ of morphine.
- Tachycardia and BP rise due to sympathetic stimulation.
- Dysphoria in high dose.
- Tolerance, physical dependence occurs with repeated doses.
- Nausea, vomiting, biliary spasm and constipation less common.
- Effective orally, high first pass metabolism.
- Irritant, so not given SC.

Butorphanol

- K analgesic more potent than pentazocine.
- Analgesia, respiratory depression less than morphine.
- Less dysphoria compared to pentazocine.
- Weak delta receptor agonist at high dose with some psychomimetic effects.
- May produce physical dependence, abuse potential is low.
- Used as IM/IV in a dose of 1–4 mg. in postoperative painful conditions.
- *Contraindication*: Cardiac ischemia.

Buprenorphine

- Synthetic thebaine congener.
- Highly lipid soluble.
- Potent analgesic 25 times more potent than morphine.
- Partial agonistic action on μ receptors, antagonistic action on k receptors.
- Slower onset and longer duration.

Nalbuphine

- K agonist, μ antagonist similar to buprenorphine; used as analgesic.
- Analgesia lasts for 6–8 hours.

- Postural hypotension occurs.
- Constipation less marked.
- Lower incidence of tolerance, physical dependence.
- Withdrawal syndrome resembles that of morphine but is milder.
- High first pass metabolism makes it orally inactive.
- Sublingual, i.m.,i.v. injection, intrathecal.
- Used in long lasting pain.

Opioid Antagonists

- Morphine derivatives with bulkier substitutions at N_{17} position.
- High affinity for μ receptor, lower affinity for other sites, e.g. δ and k.

Naloxone

- N-allyl-nor-oxymorphone.
- Competitive antagonist at all opioid receptors, more for μ receptor.
- No subjective or autonomic effects produced.
- Inert when given in absence of an agonist.
- In presence of agonist, it completely and dramatically reverses the opioid effects within 1–3 min.
- Normalization of respiration, level of consciousness, pupil size, bowel activity and awareness of pain.
- IV 0.4–0.8 mg. antagonizes action of morphine but sedation is less completely reversed.
- At 4–10 mg, it antagonizes the agonistic actions of nalorphine, pentazocine, etc. Dysphoria and psychomimetic effects are not much antagonized.
- Antagonizes the action of endogenous opioid peptides.
- Partly antagonizes the respiratory depression produced by N_2O, diazepam.
- Inactive orally due to high first pass metabolism.
- IV action starts in 2–3 min.
- *Side effects*: Uncommon rise in BP and pulmonary edema rarely occur.
- Used mainly to treat opioid-induced respiratory depression and reverse the effect of opioid during labor.

Naltrexone

- Similar to Naloxone.
- Longer duration of action (t½ 10 hrs); 1–2 days.

- Chemically related to Naloxone, pure antagonist to opioid receptors.
- Orally effective; 50 mg/day orally can be given in addicts.
- No subjective effects, craving subsides.
- Side effects: Nausea, headache; high doses can cause hepatotoxicity.

Nalmephine

- Pure opioid antagonist.
- Hepatotoxicity does not occur.
- Higher oral BA.
- Longer duration of action.

Nalorphine

- Closely related structurally to morphine.
- First specific antagonist used.
- Low doses causes antagonistic actions but at high doses analgesic action mimicked morphine.
- μ antagonist but k and δ receptor partial agonistic action.
- May precipitate withdrawal syndrome, hence not used nowadays.

Clinical Uses

1. Analgesic – pre- and postoperatively.
   - Severe headache, dysmenorrhea.
   - Labor, trauma, burn.
   - MI, renal colic.
   - Terminal disease, e.g. metastatic cancer.
2. Acute LVF.
3. Along with NSAIDs; supplemented first by weak opioids followed by strong opioid analgesic.

Drug	*Type*	*Dose*	*Dosage Form*	*Indications*
Morphine	Agonist	0.1–0.2 mg/Kg s.c. 3–4 hourly, 2–5 mg i.v. as premedicant	2–6 mg i.v., 10–15 mg i.m., 10–50 mg oral; 3–4 hrly	LVF, postoperative pain, cancer pain, pulmonary edema.
Codeine	Agonist	0.3 mg/Kg/dose as antitussive; 3 mg/kg/dose as analgesic	Cough linctus	Analgesic, cough suppressant, not recommended in children.
Pethidine	Agonist	50–100 mg i.m./s.c.	100 mg/2 ml vial, 50–100 mg tablet	Intraoperative, post-operative pain, shivering.
Tramadol	Agonist; metabolite of Trazodone	50–100 mg 8 hrly	30/100 mg tablet, 50 mg/ml 2 ml vial	Mild to moderate pain, shivering.
Pentazocine	Agonist-Antagonist	0.5–1 mg/kg/day	25 mg tablet, 30 mg/ml amp	Intraoperative, postoperative analgesic.
Naloxone	Pure Antagonist	0.2–0.4 mg i.v. at 2–3 min interval, max 4–10 mg	0.4 mg/ml, 0.04 mg/2 ml	Morphine/opioid overdose, opioid-induced respiratory depression.
Naltrexone	Pure Antagonist	50 mg/day orally	50 mg tablet	De-addiction.

Chapter

11 Pharmacotherapy of Migraine

The name 'serotonin' is derived from the vasoconstrictor substance released from a clot into the serum. Serotonin or 5 HT is considered to be an important neurotransmitter, a local gut hormone, causative agent of migraine headache as well as mediator of 'carcinoid syndrome' of carcinoid tumor and component of platelet aggregation.

Migraine is characterized by recurrent moderate to severe, throbbing unilateral headache with or without preliminary autonomic symptoms or aura. Typically the headache affects one side of the cranium, is pulsating in nature, lasting for about 2–72 hours. About 1/3 rd of patients may complain of a transient visual, sensory/motor deficit or language disturbance which signals the onset of headache, known as 'aura'. Headache may be induced by increased physical activity and may be associated with nausea, vomiting, increased sensitivity to smell, sound or light. Migraine may be associated with depression, anxiety or bipolar disorder.

Migraine may be classified into two types:

1. The 'classic' type associated with 'aura', e.g. Nausea, vomiting, visual scotoma, hemianopsia or speech abnormalities. Aura is followed by severe throbbing unilateral headache.
2. The 'common' type which is characterized by moderate to severe unilateral headache and not associated with aura.

Treatment of Migraine

1. Non-steroidal anti-inflammatory drugs—e.g. Ibuprofen, paracetamol.
2. Ergot alkaloids—Ergotamine tartrate, dihydroergotamine mesylate.
3. Triptans—Sumatriptan, rizatriptan, zolmitriptan.

TRIPTANS

The triptans are $5HT_{1A/1D}$ receptor agonists and are the mainstay in the treatment of migraine.

Triptans are indole derivatives with high affinity to $5HT_{1A/1D}$ receptor and effective in acute attack of migraine. All triptans have similar pharmacodynamic activity but different pharmacokinetics. They have no activity on other 5HT receptors/α_1, α_2, β adrenergic/dopaminergic/cholinergic receptors.

Comparison of the Pharmacological Parameters of the Triptans

Drug	*Onset of Action*	*Half Life*	*Route of Administration*	*Remarks*
Sumatriptan	1.5–2 hours	<2 hours	Oral, s.c., nasal spray; Dose: 50–100 mg	Quickest onset
Zolmitriptan	1.5–2 hours	2-3 hours	Oral	Dose: 2.5 mg
Rizatriptan	1.5–2 hours	2-3 hours	Oral	Dose: 5-10 mg
Naratriptan	2–3 hours	6 hours	Oral	Dose: 2.5 mg
Frovatriptan	2–4 hours	26 hours	Oral; Dose: 2.5 mg	Longest duration

Mechanism of Action

Migraine occurs due to abnormal dilatation of carotid arteriovenous anastomosis and shunting of carotid arterial blood flow leading to cerebral ischemia resulting in severe headache. $5HT_{1B/1D}$ agonists cause constriction of intracranial blood vessels, restoring blood flow to the brain by closing the shunts. Pro-inflammatory mediators released in the perivascular space are also prevented, e.g. release of 5HT, neurokinin, substance P, nitric oxide, CGRP, etc.

Adverse Effects

- *Oral administration*: Fatigue, asthenia, flushing, paraesthesia, tightness in chest, neck and jaw, dizziness, drowsiness, coronary artery spasm, MI, arrhythmia.
- *S.C. administration*: Pain, stinging and burning sensation.

Contraindications/Special Precautions

Uncontrolled hypertension, IHD, hepatic/renal impairment, pregnancy, epilepsy.

Drug interactions: Sumatriptan, Rizatriptan and Zolmitriptan should not be co-administered with MAO inhibitors, ergot alkaloids or other 5HT agonists.

ERGOT ALKALOIDS

- Product of Claviceps Purpura (Fungus).
- Have partial agonistic/antagonistic actions at serotonergic ($5HT_{1D}$, $5HT_2$, $5HT_3$), dopaminergic/α adrenergic receptors.
- For treatment of acute migraine attack, ergotamine tartrate and dihydroergotamine mesylate are used.
- Ergot alkaloids have restricted use for mild to moderate frequent attacks or infrequent severe attacks of migraine. As GI absorption/BA is erratic, response varies among individuals. These drugs should not be used for prolonged period.
- Ergotamine: Most effective in early attack. Administered by oral/sublingual route. Parenteral use is contraindicated. Dose: 6 mg at half hourly intervals till complete relief.
- Dihydroergotamine: It is effective in acute attack of migraine and can be administered parenterally.

Contraindications of Use

Pregnancy, peripheral vascular disease, hypertension, IHD, sepsis, hepatic/renal dysfunction, co-administration with triptans/vasoconstrictors.

OTHER DRUGS USED IN MIGRAINE

- *Beta-blockers*: Propranolol used in the dose of 40 mg/day, may be increased to a maximum dose of 160 mg/day is effective in decreasing the frequency of migraine attack.
- *Antidepressants*: Tricyclic antidepressant, e.g. Amitriptyline has been extensively used in prophylaxis of migraine specially in presence of associated depression. SSRIs have also been used successfully.
- *Calcium channel blockers*: Of the calcium channel blockers, Verapamil is commonly used. It acts by decreasing the Ca+ overload in brain due to hypoxia.
- *Anticonvulsants*: Anticonvulsants like Valproic acid is used to prevent migraine attacks but newer antiepileptic, Topiramate is found to reduce the attack rate to half.

Chapter

12 Pharmacotherapy of Substance Use Disorders

Drug dependence syndromes due to illicit drug use are often seen with:

- Stimulants—Amphetamine, Cocaine, Caffeine.
- Opiates—Morphine, Heroin.
- Sedative-Hypnotics—Benzodiazepines, Barbiturates.
- Alcohol—Ethanol.
- Psychodelic Agents—LSD, Phencyclidine.

Drug dependence may be physical or psychological. Physical dependence occurs when body adapts to the pharmacological actions of the drug and is associated with withdrawal symptoms when abruptly stopped.

Addiction means progressively out of control drug use. Withdrawal of the drug results in craving or drug seeking attitude.

Anxiety, depression, insomnia and even shyness induce people to take certain drugs for relief of such symptoms. Repeated use of the drug eventually leads to tolerance and ultimately compulsive and uncontrolled drug use leading to drug abuse. Drug abuse results more in psychiatric symptoms rather than relief of symptoms for which the drug was abused.

Sl. No.	*Drug of Abuse*	*Chronic Symptoms*	*Withdrawal Symptoms*	*Pharmacotherapy*
CNS Depressants:				
1.	Ethanol	Sedation, sleep, motor incoordination	Craving, tremor, irritation, sleep disturbances, tachycardia, hypertension, visual/auditory/ tactile hallucinations.	Diazepam/Chlorazepate/ Phenobarbitual in acute withdrawal. Detoxification – Disulfiram, naltrexone/acamprosate. Clonidine transdermal patch.
2.	Benzodiazepines Diazepam Alprazolam	Chronic use over months to years leads to increase in dose due to tolerance	Anxiety, agitation, restlessness, dizziness, vomiting and fatigue. Insomnia and nightmare.	Long acting sedative, e.g. phenobarbiital, chlordiazepoxide may be used with tapering dose. Buspirone can also be used.
3.	Barbiturate	Do, Withdrawal symptoms can be severe or fatal	Insomnia, agitation, etc. as benzodiazepine, but may lead to seizures delirium or coma.	Gradual dose reduction of the offending drug.
4.	Opioids, heroin, morphine, codeine	Anxiety, insomnia, yawning, craving	Restlessness, irritability, nausea, muscle cramps, sweating, tremor, rhinorrhea, fever, piloerection (goose skin), increase in pulse, BP, respiration, vomiting, diarrhea.	Methadone (long acting opioid) 10 mg orally stat leads to increase by 10 mg to maximum 40 mg/ day. Gradually tapered off to 5 mg/ day till total withdrawal. Clonidine oral tablets/transdermal patches. Buprenorphine can be used.

Contd...

Sl. No.	Drug of Abuse	Chronic Symptoms	Withdrawal Symptoms	Pharmacotherapy
CNS Stimulants:				
1.	Amphetamine Dextroamphetamine Methamphetamine	Normally used in ADHD, abused as euphoriant	Depression, fatigue, somnolence, hyperphagia.	Desipramine, Bupropion.
2.	Cocaine (free base alkaloid → crack)	Dose dependent. Increase in arousal, heart rate, BP, feeling of well being and increase in confidence, euphoria. Involuntary motor activity, paranoia, promiscuous sexual activity	Dysphoria, fatigue depression, sleepiness, craving, bradycardia (withdrawal → crash).	Desipramine, Imipramine, Bupropion, Venlafaxine may be used.
3.	Cannabis	Euphoria, anxiety, impaired judgement, increase in appetite, dry mouth	Insomnia, irritability, tremor, nausea, restlessness, cramps.	Lorazepam, 1 mg four hourly, haloperidol two doses of 2–5 mg orally.
4.	Hallucinogens – LSD, Mescaline	Visual illusions and hallucinations	Perceptual changes leading to frank panic attacks (bad trip).	Benzodiazepine, Diazepam 10–20 mg orally.

Drug Testing for Illicit Drug Use

Urine drug screens: Typically evaluated for cannabinoids, cocaine, opioids, amphetamine and phencyclidine. Primarily detect drugs taken within 7 days of the test.

Salivary tests for drug screening: Detect drugs taken recently within past few hours till previous three days.

Serum blood screens are most sensitive assays and detect most drugs that have been used in last 90 days.

Some drug-dosage regimens used in Alcoholism.

Drug	*Dosage*	*Alcoholism*
Diazepam	10–20 mg/4–6 hours for 3 days. Then decrease by 25% per day.	
Chlordiazepoxide	25–50 mg/4–6 hours for 2 days. Then decrease by 25% per day.	
Clonidine	0.1–0.2 mg/4–6 hours for 2 days. Then decrease by 25% per day.	Typical oral dose 0.4–0.6 mg day in 2–4 divided doses. Transdermal patch lasts one week; delivers 0.1–0.3 mg/day.
Naltrexone	50 mg/day for 3–6 months, leads to decrease in binge drinking.	
Acamprosate (Taurine analogue)	Upto 3000 mg/day in divided doses, reduction in relapse drinking and alcohol craving.	
Drug	*Withdrawal Symptoms*	*Treatment*
Phencyclidine (Angel Dust)	Behavioral changes mimicking paranoid schizophrenia. Bizarre violent behavior, increase in muscle tension, tachycardia, hypertension, drooling, nystagmus.	Seclusion, Benzodiazepine and antipsychotic, urine acidification with NH_4Cl hastens excretion.

Chapter

13 Pharmacotherapy of Dementia

Elderly patients suffering from mild, moderate or severe dementia may be suffering from Alzheimer's disease, multi-infarct dementia, dementia due to underlying disease or medical conditions like hypothyroidism, congestive cardiac failure or vitamin deficiency. Pseudodementia occurs secondary to major depression.

ALZHEIMER'S DISEASE

Symptoms

- Anterograde memory loss.
- Repetition of questions.
- Misplacement of items.
- Missed appointments.
- Forgetfulness in daily chores of life.

End stage characterized by dependence increased progression of disease to akinetic mute state. Death occurs due to pneumonia or pulmonary embolism as a complication of immobility.

Pathophysiology

Degeneration and neuronal loss is associated with amyloid plaques (extracellular accumulations of Aβ) and neurofibrillary tangles (intracellular microtubule associated protein tau). The atrophy or degeneration of cholinergic neurons leads to deficit of acetylcholine. Degeneration, however, may affect other neurotransmitters like 5HT, glutamate and neuropeptides.

Drugs Used in Treatment of Alzheimer's Disease

Sl. No.	*Drug*	*Mechanism of Action*	*Dose*	*Adverse Effects*
1.	Memantine	Non-competitive inhibition of NMDA glutamate receptor.	10 mg BD/day oral tablet; 2 mg/ml oral suspension.	Headache, dizziness.
2.	Donezepil	Reversible antagonist of cholinesterase.	10 mg OD oral.	GI distress, muscle cramps, bradycardia, abnormal dreams, fatigue.
3.	Rivastigmine	Reversible antagonist of cholinesterase; more centrally active.	3–6 mg BD oral; 9.5 mg/day transdermal patch.	GI upset; well tolerated.
4.	Galantamine	Reversible antagonist of cholinesterase, effects are sustained for at least 12 months.	8–12 mg BD oral; 16–24 mg SR, OD.	
5.	Tacrine	Old drug.	20 mg four times daily.	Hepatotoxic.

Donezepil appears to be the drug of choice; other indications are Lewy body dementia, vascular dementia and memantine is an important additional option.

HUNTINGTON DISEASE

Autosomal dominant inherited disorder associated with gradual onset cognitive disorder, motor incoordination with involuntary movements and impairment of memory, starting at the age of 35–40 years. Disease gradually progresses for 15–30 years and death ensures due to complications of immobility.

Pathophysiology

There is prominent neuronal loss in the caudate nucleus and putamen; striatal projection neurons too are affected.

Treatment

Symptomatic treatment for depression, paranoia, irritability and psychosis associated with the disease. Fluoxetine for depression and carbamazepine has been used for therapy of psychosis and paranoia.

Treatment of chorea: Tetrabenazine sedatives like benzodiazepines are also used.

Treatment of myoclonus or seizures: Clonazepam, Valproic acid.

Chapter

14 Application of Anticonvulsants and Antihistaminics in Psychiatry

ANTICONVULSANTS IN PSYCHIATRY

History

In 1950 phenytoin was found to be effective in mania as because it was found that kindling phenomenon of limbic area seizures probably had a role in development of psychosis or psychiatric symptoms. Gradually it was found that drugs like Carbamazepine and Valproic Acid were effective as mood stabilizers due to the preferential anticonvulsant action at the temporal lobe or limbic system.

Anticonvulsants Used in Psychiatry

Sl. No.	*Drug*	*Clinical Indications in Psychiatry*	*Special Remarks*
1.	Valproate	Bipolar disorder, aggression, agitation, impulsivity, acute mania, seizure disorders.	Rapid discontinuation, increase in risk of relapse in pregnancy.
2.	Carbamazepine	Acute mania, bipolar disorders, seizure disorders, panic disorders, agitation associated with dementia.	Dose should gradually be increased over 6 months. Decrease in 25% of dose in every 3 days.
3.	Lamotrigine	Bipolar disorder, unipolar depression, cyclothymia, schizoaffective disorder.	Generally well tolerated.

Sl. No.	Drug	Therapeutic Indications	Starting Dose (mg)	Dose Range (mg/day)	Blood Level (mg/ml)	Special Remarks
1.	Pregabalin	Post-herpetic neuralgia, Neuropathic pain, Fibromyalgia, Diabetic neuropathy, Generalized anxiety disorder, panic disorder, social anxiety.	50	100–300	24–48	No D/I, renal excretion.
2.	Tiagabine	Anxiolytic, hypnotic resistant to other drugs, anti-convulsant.	1	4–32	—	Lower doses should be used in hepatic dysfunction.
3.	Gabapentin	Panic attack, social anxiety disorder, reduction in alcohol craving, adjunct to mood stabilizer, post-herpetic neuralgia, neuropathic pain.	100	400–1200	6–21	No drug interactions, renal excretion.
4.	Levetiracetam	Acute mania, anxiolytic, add on with antidepressants.	250	500–2000	—	Non-hepatic hydrolysis and renal excretion.
5.	Topiramate	Primary alcoholism, Post-traumatic stress disorder, borderline personality disorder, binge eating disorder, neuropathic pain, migraine.	25	200–1000	3–5	Induces CYP3A4 Drug Interactions.
6.	Zonisamide	Acute mania, drug-induced weight gain.	25-100	100–600	15–40	Sulfonamide, may cause hypersensitivity reactions, blood dyscrasia.

CONCLUSION

Other anticonvulsants like oxcarbazepine, ethosuximide may have a role in bipolar disorders and other psychiatric disorders but their use as monotherapy has not been justified. So, they have an adjunctive role in most psychiatric disorders.

ANTIHISTAMINICS IN PSYCHIATRY

Indications of use in psychiatry

- Neuroleptic induced Parkinsonism.
- Neuroleptic induced acute dystonia.
- As hypnotic.
- As anxiolytic.
- Anorexia nervosa.

H_1 Receptor Antagonists Commonly Used in Psychiatry

Sl. No.	*Drug*	*Route*	*Dose*	*Dosage Form*	*Common Indication*
1.	Diphen-hydramine	Oral	25–50 mg QDS	Capsules, tablet 25 mg, 50 mg, liquid 12.5 mg/ml.	Neuroleptic induced Parkinsonism, neuroleptic induced dystonia.
2.	Hydroxyzine	Oral	50–100 mg TDS/ QDS IM	Tablet 10/25/50/100 mg, syrup 10 mg/5 ml, 25–50 mg/ml.	Sedative, anxiolytic, pruritus. Do
3.	Promethazine	Oral	50–100 mg TDS/ QDS	15.2/25/50 mg tablets.	Sedative, anxiolytic.
4.	Cyproheptadine	Oral	4–20 mg/day	4 mg tablet, syrup 2 mg/5 ml.	Anorexia nervosa, drug-induced orgasmic disorders.

Chapter

15 Psychiatric Drug Therapy in Special Situations

PREGNANCY

None of the psychotropic drugs are completely safe during pregnancy or lactation. The risk and benefit ratio needs to be weighed on individual situations. The US FDA rates drugs used in psychiatry into five categories according to its safety in use during pregnancy.

Category	*Definition*	*Examples*
A	No fetal risks in controlled human studies.	Iron
B	No fetal risks in animal studies but no controlled human studies.	Clozapine
C	Adverse fetal effects in animals but no human data available.	Lamotrigine Gabapentin, SSRI, SGA
D	Human fetal risk seen.	TCA, benzodiazepine, lithium
E	Proved fetal risk in humans.	Valproic acid, thalidomide

Risks of drug administration during pregnancy occurs specially in first trimester due to teratogenesis or behavioral teratogenesis. All psychotropic drugs cross placenta to some extent. Fetus may also be affected in late pregnancy, labor delivery and during lactation.

Examples of some teratogenics:

- Valproate—Neural tube defects.
- Carbamazepine—Neural tube defects, minor anomalies.
- Lithium—Cardiac anomalies specially Ebstein's anomaly, behavioral effects.

Guidelines of Drug Therapy during Pregnancy and Lactation

- Stop psychotropic medication 2–3 weeks before pregnancy if possible to avoid malformation.
- Medications to be avoided in first trimester of pregnancy.
- Medication may be withdrawn carefully a few weeks before delivery in some circumstances.
- Whenever possible drug therapy is to be avoided in patients who become pregnant or who intends pregnancy.
- All SSRIs except Paroxetine (potential cardiac anomalies like ASD) have been classified under category C agents.
- Most anticonvulsants are teratogenic but the newer anticonvulsants like lamotrigine, gabapentin, topiramate are in category C of FDA.
- Second Generation Antipsychotics except Clozapine (category B) fall under category C and may not be teratogenic but carries the risk of gestational diabetes.
- The hypnotic benzodiazepines are contraindicated in pregnancy and are categorized in Group X.
- Cocaine and alcohol intake in pregnancy may not produce physical anomalies but may be associated with behavioral problems in child development.
- All known psychoactive drugs are secreted in breast milk but the concentration in milk is much lower than that of drug level in maternal blood.
  Sertraline may be used in treatment of postpartum depression and though only trace amount of the drug is found in the nursing infant, child should be watched for irritability or sedation during therapy.
- Postpartum depression/baby blues developing within 12 weeks of delivery are often managed by counselling and support.
- Postpartum psychosis develop within days or within 2–3 weeks following delivery. Second generation antipsychotics in combination with antidepressants are often necessary.

PEDIATRIC/YOUNG ADOLESCENT AGE GROUP

Sufficient data regarding effect of psychotropic drugs in children or adolescents on brain function, behavior or future physical health in adulthood has not yet been established. So, FDA approval of use of standard psychiatric drugs in children or adolescent age group is not existent.

Use of D-amphetamine and methylphenidate in attention deficit or hyperactivity disorder in children have been studied. It was found to affect body growth, e.g. 1–3 cm in height throughout the period of development.

Drugs Used in ADHD

Drugs	*Indications*	*Comments*
Methylphenidate (beyond 6 yrs)	18–54 mg/day, transdermal patch OD	Anorexia, insomnia, dysphoria, tics.
Dextroamphetamine (beyond 3 yrs)	2.5 mg BD/day → 40 mg BD/QDS/day	Sleep disturbance.
Desipramine (beyond 12 yrs)	10–25 mg QDS	—
Bupropion (children, adolescents)	3–6 mg/kg/day	Anorexia, risk of seizures.
Atomoxetine (beyond 6 yrs)	1.2 mg/kg/day – 1.8 mg/kg/day	Decrease in body weight, increase in heart rate, BP.
Modafinil (beyond 16 yrs)	300–400 mg/day	Headaches, mild GI symptoms.

Antipsychotics in Children

Drugs	*Indications*	*Comments*
Second Generation Antipsychotics, e.g. Aripiprazole Risperidone	Indicated in childhood schizophrenia 2–10 mg/day 1–2 mg/day (Age beyond 13 yrs)	Akathesia, Dystonia. Weight gain (For mixed manic episodes used in >10 yr old, For autism used in 6–17 years old).
First Generation Antipsychotics in low dose, e.g. Haloperidol (>3 yr old) Pimozide (>12 yr old)	Indicated in tics of Tourette's disorder, Autism, violent behavior 0.5–3 mg/day 2–10 mg/day	May affect learning process, sedation, dystonia, cognitive blunting.

Antidepressants in Children

Blackbox warning on use of antidepressants in children. It leads to increase in risk of suicidal thoughts.

Drugs	*Indications*	*Comments*
SSRIs Fluoxetine (8-18 yrs)	Childhood depression 5 mg/day → 3 mg/day gradually increase in 1–2 weeks.	Adverse effects are similar to those in adults.
Fluvoxamine (8–17 yrs) Sertraline (>6 yrs)	Childhood OCD.	
TCA-Imipramine (beyond 6 yrs)	0.3–1.0 mg/kg/day in Enuresis.	

Mood Stabilizers in Children and Adolescents

Drugs	*Indications*	*Comments*
Lithium Dose 150-300 mg/day (in > 12 yr old)	Mania, bipolar disorder, co-morbid substance abuse explosive, violent behavior.	Children have increase in renal clearance and better tolerance compared to adults.
Valproate Dose 15-60 mg/kg/day (in>10 yr old)	Aggressive behavior in adolescents.	Children less than 2 years, increase in risk of hepatotoxicity.
Carbamazepine Dose 10-50 mg/kg/day in divided doses (in >6 yr old)	Bipolar mood disorder.	Anticonvulsants show increase in risk of hepatotoxicity in children.

Anti-anxiety Drugs in Children

Drugs	*Indications*	*Comments*
Zolpidem (6-17 yrs)	Pavor nocturnus/sleep walking.	Somnambulism, Amnesia.
Alprazolam (safety not established)	Panic disorder, generalized anxiety disorder, avoidant personality.	If used in daytime, may increase activity or aggravate behavior disorders.
Buspirone (6-17 yrs)	Childhood anxiety disorders.	---

Drug therapy in children requires close monitoring and close collaboration of parents, physician, teachers or caretakers. Gradual increase in dose of drugs over weeks to be carried out in long-term treatment.

Geriatric Psychopharmacology

- Low serum protein level results in relatively higher free drug level in blood.
- Elderly patients are more prone to peripheral effects like hypotension, constipation and CNS effects like delirium, tremor compared to adults.
- Decreased hepatic and renal function also results in higher blood concentration of drug and increase in probability of adverse effects.
- Drug therapy should always be started at minimum therapeutic dose and increased gradually under close monitoring.

Antidepressants

- SSRIs specially sertraline, citalopram, escitalopram are first line drugs in geriatric depression.
- All TCAs are more prone to produce anticholinergic side effect and orthostatic hypotension.
- Next to SSRIs, Venlafaxine or Nortriptyline may be used in more serious depressive conditions.
- Daytime hypotension or orthostatic hypotension is a problem in patients treated with Trazodone while hepatotoxicity limits the use of Nefazodone.
- Modafinil may be of benefit as adjunctive therapy to standard antidepressants in a dose of 100–200 mg/day in the morning.

Hypnotics and Sedatives

- Elderly patients are more prone to impaired cognition and falls.
- Benzodiazepine metabolism is slowed in elderly and long acting benzodiazepines often cause day time sleepiness.
- Newer benzodiazepines, e.g. Zaleplon in the dose of 0.5 mg at night or eszopiclone in the dose of 1–2 mg at night may be more advantageous due to low abuse potential. Minimum drug interactions and lack of hangover effect.
- Ramelteon is a good choice as hypnotic in elderly as it does not contribute to confusion, amnesia or orthostatic hypotension.

Mood Stabilizers

- Lithium, if used, should be started at minimum dose of 300 mg/day.

- Strict monitoring of TDM should be done.
- Concurrent drug administration may lead to drug interactions.
- Valproate seems to be better tolerated compared to lithium, given at a low dose of 250 mg/day.
- Carbamazepine use may lead to several drug interactions and usually avoided in elderly.

Antipsychotics

- Lower doses should be used as blood levels are 1.5–2 times higher in elderly compared to adults.
- Quetiapine even at higher doses carries low risk of EPS, hence preferred.
- Anticholinergic effects of Clozapine are poorly tolerated by elderly.
- Aripiprazole, Risperidone and Olanzapine are other alternatives to Quetiapine.
- There is increased risk of mortality in elderly with dementia treated with second generation anti-psychotics. Hence, use of anti-psychotics in presence of dementia should be avoided.
- In agitated patients with dementia, Valproate 500–800 mg/day or Oxazepam, Benzodiazepine of simple metabolism and low abuse potential may be tried.

Chapter

16 Neuropsychiatric Disorders due to Drugs or Medical Illness

MEDICAL CONDITIONS ASSOCIATED WITH PSYCHIATRIC SYMPTOMS

- *Cushing's syndrome*: Depression, Insomnia, Mania, Psychosis, Suicidality.
- *Adrenocortical insufficiency*: Lethargy, Depression, Psychosis, Delirium, Fatigue.
- *Hyperparathyroidism*: Depression, Paranoia, Confusion.
- *SLE*: Depression, Psychosis, Delusion, Hallucination.
- *Wilson's disease*: Mood disturbances, Delusions, Hallucination.
- *Thiamine deficiency*: Confusion, Confabulation.
- *Pyridoxine deficiency*: Apathy, Irritability.
- *Vitamin B_{12} deficiency*: Irritability, Inattentiveness, Psychosis, Dementia.
- *Hepatic encephalopathy*: Euphoria, Disinhibition, Psychosis, Depression.
- *Pheochromocytoma*: Anxiety, Apprehension, Fear of impending doom.

Drug-induced Psychotic Disorders

- Reserpine, Methyldopa → Depression.
- Propranolol → Lethargy, Major depression.
- Benzodiazepines, Barbiturates → ADHD, Memory disturbances in elderly.
- Psychostimulants → Aggravate schizophrenia, Mania.
- Steroids, Levodopa → Delirium, Paranoid Psychosis, Mania, Depression, Anxiety.
- Anti-Parkinsonism Drugs → Hallucinations, Confusion.
- Anticholinergics → Delirium, Confusion.

Body Weight Disorders

Weight gain is often associated with psychotropic drug therapy specially antidepressants, antipsychotics or mood stabilizers. It may also be associated with binge eating disorders.

Obesity is defined as BMI > 30 kg/m^2. Obesity, whatever may be the cause, is associated with increasing risk of—coronary artery disease, hypertension, diabetes type 2, gall stones, cancer, pulmonary abnormalities, e.g. sleep apnea, bone and joint disease, gout and is of concern.

Medications approved for weight loss acts either by decrease in appetite, increase in satiety or decrease in GI absorption. Hence they act by:

- suppression of appetite, e.g. amphetamine.
- increasing body's metabolism, e.g. Thyroid hormones.
- interfering with absorption of nutrients like carbohydrate or fat.

A. Appetite suppressants: These act by increasing neurotransmitter bioavailability of NE, serotonin or dopamine.

i. Sympathomimetic agents—benzamphetamine, phentermine, diethylpropion, phendimetrazine.
Contraindications: Hypertension, narrow angle glaucoma, renal/hepatic impairment.
Side effects: Dry mouth, euphoria, palpitation, hypertension, constipation.

ii. Serotonergic agents—Fenfluramine, Dexfenfluramine.
Serotonergic drugs were first used but was withdrawn due to high incidence of valvular disease, pulmonary hypertension.
SSRIs—Fluoxetine 60 mg, Sertraline 50–200 mg.

iii. Mixed serotonergic and nor-adrenergic agent.
Sibutramine—10–15 mg/day acts by inhibiting both 5HT and NE reuptake. Also stimulates thermogenesis by β_3 activation.
Side effects: Anorexia, constipation, insomnia, dry mouth, hypertension.

B. Thermogenic agents: Act by increasing body's metabolism.
Ephedrine + Caffeine combination
Sibutramine
Thyroid hormones

C. Digestive inhibitors: Orlistat – lipase inhibitors.
Mechanism of action: Potent and irreversible inhibition of gastric and pancreatic lipases.

Adverse effects: Oil spitting, fecal urgency, steatorrhea, flatulence, abdominal pain.

D. Fat substitute: Olestra – sucrose polymer used as fat substitute. *Adverse effects*: Loose stools, bloating, flatulence. Fat soluble vitamins need supplements.

E. Others:

Bupropion (atypical antidepressant), Topiramate—antiepileptic, often used in combination with phentermine but produces cardiovascular and CNS adverse effects, specially affecting cognition.

Rimonabant—cannabinoid 1 receptor antagonist, acts centrally by reducing appetite.

Neuropeptide Y, Cholecystokinin,

Metformin—oral anti-diabetic agent with anorectic property,

Lorcaserin—$5HT_{2c}$ receptor agonist, increasing weight loss by decreasing appetite and increasing satiety,

Exenatide—Long acting GLP 1 analogue, delaying gastric emptying, increasing satiety and decreasing appetite,

Pramlintide—Synthetic analogue of hormone Amylin, delaying gastric emptying and increasing satiety.

Appetite Stimulants

These drugs are often necessary to be prescribed in anorexia, cachexia or chronic unexplained weight loss.

- Megestrol, Medroxyprogesterone—Progesterone used in anorexia or unexplained weight loss.
- Oxandrolone—Anabolic steroid as adjunct in treatment of chronic weight loss.
- Dronabinol—Cannabinoid used in the treatment of AIDS-related cachexia.
- Antidepressants—Amitriptyline, Mirtazapine.
- Anticonvulsants—Gabapentin, Pregabalin.
- Antihistaminic—Cyproheptadine.
- Corticosteroids—Dexamethasone, Prednisone, Hydrocortisone.

The use of appetite stimulants to produce weight gain is controversial though it might sometimes be necessary to implement in cachexia in elderly or unexplained weight loss.

Chapter

17 Psychiatric Emergencies

Sl. No.	*Clinical Condition*	*Emergency Management*
1.	Delirium tremens	• Chlordiazepoxide 25–50 mg QDS × 2 days parenterally then 15–100 mg oral • Haloperidol may be added for psychotic symptoms.
2.	Alcohol withdrawal	• Maintenance of fluid and electrolytes and monitoring of vital signs • Benzodiazepines, e.g. Diazepam 2–10 mg • Thiamine 100 mg IM.
3.	Benzodiazepine intoxication	• Supportive measures • Flumazenil 7.5–45 mg/day.
4.	Anticholinergic intoxication	• Discontinue the drug • Physostigmine 0.5–2 mg for severe agitation.
5.	Hallucinogen-induced psychotic disorder	• Benzodiazepines, Diazepam, 2–20 mg orally, reassurance.
6.	Lithium toxicity	• Lavage with wide-bore tube, osmotic diuresis; ICU treatment, if required.
7.	Neuroleptic malignant syndrome	• Discontinue antipsychotic • IV dantrolene sodium 1 mg/kg/day × 8 days • Bromocriptine 2.5 mg orally • Hydration and proper cooling • Monitoring of blood creatine phosphokinase (CPK) level.
8.	Acute onset panic disorder	• Propranolol 10–30 mg • Alprazolam 0.25–2 mg • ECG to exclude mitral valve prolapse.
9.	Stupor/Catatonic syndrome	• Supportive measures A, B, C, etc. specially airway

Contd...

Sl. No.	*Clinical Condition*	*Emergency Management*
		• 50 ml of 50% Dextrose or 2 ml/kg body weight for children (for hypoglycemia) • Naloxone 0.4 mg IV (morphine poisoning) • Physostigmine 1–2 mg IV (anti-cholinergic poisoning) • Thiamine 100 mg IV (Wernicke's encephalopathy) • Hydrocortisone 100 mg IV (adrenal crisis) • L-Thyroxine 200–500 mg IV (myxedema coma) • Flumazenil 0.2 mg IV (benzodiazepine toxicity).
10.	Akathisia (agitation, restlessness, dysphoria)	• Reduce antipsychotic dosage • Propranolol 30–120 mg/day • Benzodiazepine, Diphenhydramine oral/IV.
11.	Delirium	• Investigate the cause • Benzodiazepines • Low dose high potency antipsychotic after proper evaluation.
12.	Acute Dystonia (acute involuntary spasm of muscles of neck, jaw, tongue, face, eyes, even trunk)	• Decrease dose of antipsychotic • Diphenhydramine or Benztropine IM.
13.	Hyperventilation (clouded consciousness, blurred vision, anxiety, tremor)	• Correction of alkalosis • Patient counselling • Tranquilizers.
14.	Excited or Violent behavior	• Diazepam 5–10 mg or Lorazepam 1–2 mg parenterally • Haloperidol 2–10 mg parenterally in psychosis • Restrain ECT only as a last resort.

Drug-induced Movement Disorders Causative Agents

- Phenothiazine – Fluphenazine
  Perphenazine
- Thioxanthenes – Thiothixene
- Butyrophenones – Haloperidol
  Droperidol
- Diphenylbutylpiperidine – Pimozide
- Second generation antipsychotics – Risperidone, Aripiprazole
- Non-psychotropic drugs – Metoclopramide,
  Prochlorperazine

Drugs used in the Treatment of Extrapyramidal Symptoms (EPS)

- Anticholinergics – Benztropine, Biperiden,
  Procyclidine,
  Trihexyphenidyl
- Antihistaminics – Diphenhydramine
- Amantadine
- β-blocker – Propranolol
- α receptor antagonist – Clonidine
- Benzodiazepine – Clonazepam, Lorazepam,
  Buspirone
- Vitamin E

Sl. No.	*Drug*	*Daily Dosage*
1.	Benztropine	0.5–2 mg TDS orally 1–2 mg IM/IV
2.	Biperiden	2–6 mg TDS orally 2 mg IM/IV
3.	Trihexyphenidyl	2–5 mg TDS orally
4.	Diphenhydramine	25 mg QDS orally 25 mg IM/IV
5.	Propranolol	20–40 mg TDS
6.	Clonidine	0.1 mg TDS orally
7.	Clonazepam	1 mg BD orally
8.	Lorazepam	1 mg TDS orally
9.	Buspirone	20–40 mg QDS orally
10.	Vitamin E	1200–1600 IU/day

Chapter

18 Drug-Drug Interactions

Psychotropic drug-drug interactions are of importance to the practising psychiatrist. These interactions if kept unaware, may lead to complications which at times may even be fatal. Drug interactions may be:

Pharmacodynamic, e.g. Amitriptyline and Benztropine resulting in enhanced anticholinergic adverse effects or MAOI and SSRI resulting in hypertensive crisis, or

Pharmacokinetic, e.g. CYP450 enzymes induction or inhibition, p glycoprotein, an ATP dependant extruding transporter induction or inhibition, or absorption, distribution or excretion of drug altered due to coadministration of another drug, e.g. action of Benzodiazepine may be prolonged when co-administered with microsomal enzyme inhibitor INH or cimetidine; Carbamazepine a microsomal enzyme inducer may decrease the efficacy of Haloperidol; absorption of Ziprasonidone may be enhanced by presence of food.

Most of the psychotropic drugs are either inhibitor or inducer of a variety of CYP450 enzymes resulting in a myriad of drug interactions, which needs a brief discussion.

Substrates, Inhibitors, and Inducers of Major Cytochrome Isozymes for Psychotropic Drugs

Enzyme	*Substrate*	*Inhibitors*	*Inducers*
CYP2D6	**Antipsychotics:** Fluphenazine, perphenazine, thioridazine, haloperidol, chlorpromazine, clozapine, risperidone, olanzapine, aripiprazole, iloperidone, zuclopenthixol **Antidepressants:** Citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine,	Bupropion Duloxetine Paroxetine Fluoxetine	Not known

Contd...

Enzyme	*Substrate*	*Inhibitors*	*Inducers*
	amitriptyline, nortriptyline, clomipramine, desipramine, imipramine, mirtazapine, venlafaxine		
CYP3A4	**Antipsychotics:** Haloperidol, pimozide, clozapine, risperidone, quetiapine, ziprasidone, aripiprazole, iloperidone, lurasidone **Antidepressants:** Citalopram, escitalopram, amitriptyline, clomipramine, imipramine, mirtazapine, nefazodone, sertraline, venlafaxine **Anxiolytics:** Alprazolam, clonazepam, diazepam, buspiron **Sedatives/hypnotics:** Zolpidem, zaleplon, flurazepam, triazolam	Nefazodone	Carbamazepine
CYP1A2	**Antipsychotics:** Haloperidol, chlorpromazine, perphenazine, thioridazine, clozapine, olanzapine, asenapine, pimozide, loxapine, thiothixene, trifluoperazine **Antidepressants:** Fluvoxamine, amitriptyline, clomipramine, imipramine, duloxetine, mirtazapine	Fluvoxamine	Carbamazepine
CYP2C9	Valproic acid	Fluoxetine Fluvoxamine	Carbamazepine
CYP2C19	**Antipsychotics:** Clozapine **Antidepressants:** Citalopram, escitalopram, clomipramine, imipramine, amitriptyline	Fluvoxamine	Carbamazepine

ANTIDEPRESSANTS

SSRIs

Drug	*CYP 450 Enzyme Inducer (↑) Inhibitor (↓)*	*Drugs Which Interact*	*Special Remarks*
Fluoxetine	↓2D6, 3A4	Atomoxetine, bupropion, MAOIs, mirtazapine, TCA, clozapine, nefazodone, typical antipsychotics, risperidone, reboxetine, duloxetine, phenytoin, carbamazepine	Can add Olanzapine in BPD, Trazodone for insomnia.
Citalopram, Escitalopram	mild ↓ in 2D6	Tramadol, secondary amineTCAs, MAOIs, anticoagulants, phenytoin, carbamazepine, codeine, beta blockers, thioridazine, pimozide	SIADH, hyponatremia in elderly, sexual dysfunction are common.
Paroxetine	↓ 2D6	MAOIs, anticholinergics, TCAs, theophylline, warfarin, β-blockers, thioridazine, triptans, bupropion, duloxetine, nefazodone, risperidone	Caution in seizures, BPD.
Sertraline	↓ 2D6, 1A2, 3A4 (Dose related)	Statins, pimozide, MAOIs, warfarin, NSAIDs, TCA, triptans, thioridazine, bupropion, carbamazepine, phenytoin, lamotrigine	Sexual dysfunction, hyponatremia in elderly, sweating.
Fluvoxamine	↓ 1A2, 2C19	Bupropion, carbamazepine, clozapine, duloxetine, MAOIs, thioridazine, mirtazapine, olanzapine, pimozide, tizanidine, alosetron, ramelteon	Sedation/ insomnia, seizures, sweating, sexual dysfunction.

SNRIs

Drug	*CYP 450 Inhibitor/ Inducer*	*Drugs Which Interact*	*Special Remarks*
Duloxetine	mild↓2D6	TCA, MAOIs, theophylline, fluvoxamine, fluoxetine, paroxetine, bupropion, carbamazepine	Caution in liver disease, alcoholic.
Venlafaxine		MAOI, anticoagulants, tramadol, triptans, codeine, cimetidine	Contraindication in heart disease, hypertension.

TCAs

Drug	*CYP 450*	*Drugs Which Interact*	*Special Remarks*
Imipramine	↓2D6, ↓p glycoprotein	Anticholinergics, fluoxetine, paroxetine, duloxetine, fluvoxamine, sympathomimetics, bupropion, pimozide, sertraline, ziprasonidone, citalopram, escitalopram, carbamazepine, phenytoin, MAOIs, phenothiazines, haloperidol, clonidine	Contraindication in MI, QTc prolongation, arrhythmia.
Desipramine	Do	Do	Do
Clomipramine	Do	Do	Do

5HT2 Antagonists

Drug	*CYP 450 Enzyme*	*Drugs Which Interact*	*Special Remarks*
Nefazodone	Inhibits CYP3A4, induces p glycoprotein	MAOIs, SSRIs, alprazolam, triazolam, buspirone, statins except pravastatin/fluvastatin, pimozide, haloperidol, general anesthetics, carbamazepine	Hepatotoxic, caution in seizures, BPD.

Contd...

Drug	*CYP 450 Enzyme*	*Drugs Which Interact*	*Special Remarks*
Trazodone	Induces p glycoprotein	Antihypertensives, specially clonidine, SSRIs, MAOIs, digoxin, phenytoin, warfarin, CNS depressants	Seizures, BPD, erectile dysfunction.

Tetracyclic Antidepressants

Drug	*P450 Inducer/ Inhibitor*	*Drugs Which Interact*	*Special Remarks*
Bupropion	Inhibits 2D6	TCAs, MAOIs, tramadol, codeine, carbamazepine β-blockers, thioridazine, atomoxetine, sertraline, duloxetine, fluoxetine, fluvoxamine	Caution in seizures, CNS tumor, h/o insomnia/weight loss.
Amoxapine	Metabolized by 2D6	MAOIs, SSRIs, phenothiazines, sympathomimetics, drugs causing QTc prolongation	Weight gain, EPS, caution in hypokalemia, seizure, MI, bradycardia.
Maprotiline	Metabolized by 2D6	Drugs ↑QTc interval (pimozide, thioridazine, moxifloxacin, sparfloxacin), β-blockers, calcium channel blockers, digitalis, clonidine, phenothiazines	Rapid onset of action, caution in electrolyte imbalance, h/o MI, seizures.
Mirtazapine	No induction/ inhibition	MAOIs, tramadol, no significant drug interactions	May ↑cholesterol, ↑weight, caution in history of seizures.

MAO Inhibitors

Drug	*CYP 450 Induction/ Inhibition*	*Drugs Which Interact*	*Special Comments*
Phenelzine	Inhibits 2A6, 1A2, 2C19, 2E1	SSRIs, sympathomimetics, other MAOI, CNS depressants, TCAs, alcohol, mirtazapine, carbamazepine	Hypoglycemia in diabetics, Contraindication in CVD/ cerebrovascular disease, pheo-chromocytoma.
Tranylcypromine	As above	As above	As above

Typical Antipsychotics

Drugs	*CYP 450 Enzyme Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Phenothiazines; e.g. thioridazine	2D6 inhibition, p glycoprotein↓	Fluoxetine, fluvoxamine, paroxetine, duloxetine, bupropion, sertraline, citalopram, propranolol, pindolol, CNS depressants, lithium	Recent MI, QTc prolongation, EPS, priapism; ↑chance of arrhythmia and sudden death.
Haloperidol	Same as above	Levodopa, dopamine agonists, antihypertensives, anticholinergics, TCAs, CNS depressants, phenytoin, fluvoxamine, carbamazepine	Weight gain, EPS, ↑risk of QTc prolongation/ torsades de pointes.

Contd...

Drugs	*CYP 450 Enzyme Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Pimozide	2D6, 3A4 inhibition, p glyco-protein↓	Levodopa, dopamine agonists, drugs prolonging QTc interval, antihypertensives, fluoxetine, sertraline, fluvoxamine, nefazodone, CNS depressants, lithium	QTc prolongation, EPS, ↑body weight, caution in elderly

Atypical Antipsychotics

Drugs	*CYP 450 Enzyme Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Aripiprazole	No induction/ inhibition, Metabolized by 3A4 and 2D6	Nefazodone, ketoconazole, fluvoxamine, fluoxetine, carbamazepine, phenytoin, other antipsychotics	No risk in BPD, diabetes, dyslipidemia, minimum weight gain; caution in CVD, glaucoma, arteriosclerosis.
Clozapine	Mild inhibitor of 2D6; Metabolized by 1A2, 2D6 and 3A4	Antihypertensives, MAOIs, aripiprazole, carbamazepine, phenytoin, fluvoxamine, fluoxetine	Caution in myocarditis, cardiomyopathy, glaucoma, drugs causing agranulocytosis.
Olanzapine	P glycoprotein inhibitor	Antihypertensives, levodopa, dopamine agonists, fluvoxamine, carbamazepine, tobacco, phenytoin, aripiprazole	Caution in hypotensive states, glaucoma, paralytic ileus, prostatic hypertrophy.

Contd...

Drugs	*CYP 450 Enzyme Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Quetiapine	P glycoprotein inhibitor	Antihypertensives, CYP 3A4 and 2D6 inducers	Caution in hypotensive states, elderly, prolonged QT interval, CVD, cerebrovascular disease.
Risperidone	2D6 inhibitor	Antihypertensives, levodopa, dopamine agonists, fluoxetine, paroxetine, clozapine, phenytoin, carbamazepine	Caution in hypotensive states, aspiration pneumonia, dysphagia, diabetes, dyslipidemia, hyperprolactinemia, atrial fibrillation.
Ziprasonidone	No induction/ inhibition	Antihypertensives, levodopa, dopamine agonists, antiarrhythmics	Caution in QTc prolongation, hypotensive states, dysphagia, aspiration pneumonia.

Mood Stabilizers

Drugs	*CYP 450 Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Carbamazepine	Inhibitor of 2C19, inducer of 3A4, 1A2, 2B6, 2C8/9, UGT 1A4	3A4 inhibitors (nefazodone, fluoxetine, fluvoxamine), clomipramine, phenytoin, primidone(↑), clozapine, benzodiazepines, dicoumarol, warfarin, haloperidol, ethosuximide, tiagabine, valproate, OCP(↓), lithium, CNS depressants	Risk of aplastic anemia, agranulocytosis, glaucoma, SIADH.

Contd...

Drugs	*CYP 450 Induction/ Inhibition*	*Drugs Which Interact*	*Special Remarks*
Lamotrigine	Metabolized like valproate	Valproate, enzyme inducing antiepileptics, OCPs. BEST TOLERATED MOOD STABILIZER	Rashes; of choice in bipolar depression.
Lithium	Not Metabolized, no induction/ inhibition	Diuretics specially thiazides, NSAIDs, COX-2 inhibitors, ACE inhibitors, metronidazole, methyl dopa, carbamazepine, phenytoin, calcium channel blockers, SSRI, haloperidol, NM blocking agents	Ataxia, tremor, dysarthria, DI, memory deficit, weight gain, arrhythmia.
Oxcarbazepine	Inducer of 3A4, UGT 1A4	CNS depressants, MAOIs, CYP450 enzyme inducers, verapamil, phenytoin, OCP, dihydropyridine calcium channel blockers	Hyponatremia, sedation, rash, diplopia, vertigo.
Phenytoin	Inducer of 2B6, 2C9/19, 3A4, UGT 1A1,1A4	Carbamazepine, phenobarbitone, INH, topiramate, fluoxetine, fluconazole, digoxin, quinidine, steroids, OCPs, cyclosporine, etc.	Nystagmus, ataxia, diplopia, gingival hyperplasia, osteoporosis, lympha-denopathy, agranulocytosis.
Topiramate	Inhibitor of 2C19, mild inducer of 3A4	Metformin, carbamazepine, phenytoin, valproate, OCP, carbonic anhydrase inhibitors, CNS depressants	Weight loss, risk of metabolic acidosis, kidney stones.
Valproate	Inhibitor of 2C9	Lamotrigine, CYP 450 enzyme inducers, aspirin, clonazepam, topiramate, fluvoxamine, fluoxetine, cimetidine, erythromycin, ibuprofen	Hepatotoxicity, pancreatitis, teratogenicity.

Outcome-based Classification of Severe Psychotropic CYP Interactions

Sl. No.	*Involved Drugs*	*Involved CYP Isozymes*	*Mechanism*	*Outcome*
1.	Fluoxetine and paroxetine	CYP2D6	Inhibitors	Severe bradycardia, atrioventricular block
	Metoprolol	CYP2D6 and CYP3A4	Substrate	
2.	Fluvoxamine	CYP1A2, CYP2C19 and CYP2C9	Inhibitor	Increase in INR and risk of severe bleeding
	Warfarin	CYP1A2, CYP3A4, CYP2C9 and CYP2C19	Substrate	
3.	Fluoxetine and paroxetine	CYP2D6	Inhibitors	Pathologic bradycardia and hypotension
	Carvedilol	CYP2D6 and CYP2C9	Substrate	
4.	Duloxetine, fluoxetine and paroxetine	CYP2D6	Inhibitors	Rebound arrhythmias, ataxia, nausea, vomiting, and heartburn
	Mexiletine	CYP2D6 and CYP1A2	Substrate	
5.	Fluvoxamine	CYP1A2 and CYP2C9	Inhibitor	Bradycardia, hypotension, and cardiac arrhythmias
	Verapamil	CYP1A2, CYP3A4 and CYP2C9	Substrate	
6.	Fluvoxamine	CYP2C9	Inhibitor	Hypotension, severe dizziness and fainting
	Losartan	CYP2C9 and CYP3A4	Substrate	

Outcome-based Classification of Moderate Psychotropic CYP Interactions

Sl. No.	Involved Drugs	Involved CYP Isozymes	Mechanism	Outcome
1.	Duloxetine, fluoxetine and paroxetine	CYP2D6	Inhibitors	Failure of breast cancer therapy
	Tamoxifen	CYP2D6, CYP3A4 and CYP2C9	Substrate	
2.	Fluvoxamine	CYP2C19	Inhibitor	Failure of anticonvulsant therapy
	Primidone	CYP2C19	Substrate	
3.	Pioglitazone	CYP3A4	Inducer	Decreased antipsychotic therapeutic efficacy
	Clozapine	CYP1A2, CYP3A4, CYP2D6 and CYP2C19	Substrate	
4.	Prednisone and rifampin	CYP2C19	Inducers	Failure of antidepressive treatment
	Citalopram and escitalopram	CYP2C19, CYP3A4 and CYP2D6	Substrates	
5.	Smoking and St. John's wort	CYP1A2	Inducers	Decreased antipsychotic therapeutic efficacy
	Clozapine	CYP1A2, CYP3A4, CYP2D6 and CYP2C19	Substrate	

Outcome-based Classification of Mild Psychotropic CYP Interactions

Sl. No.	Involved drugs	Involved CYP Isozymes	Mechanism	Outcome
1.	Erythromycin	CYP3A4	Inhibitor	Somnolence, headache and nausea
	Hypnotic sedatives	CYP3A4	Substrates	
2.	Paroxetine and fluoxetine	CYP2D6	Inhibitors	Marked reduction in analgesic effect
	Hydrocodone	CYP2D6	Substrate	
3.	Fluvoxamine	CYP1A2	Inhibitor	Anxiety and palpitation
	Caffeine	CYP1A2	Substrate	

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